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SEROLOGIC RESPONSE OF INFANTS AND PRESCHOOL CHILDREN TO POLIOMYELITIS VACCINE

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and
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• *Several lots of poliomyelitis vaccine were used in a study of the serologic responses of 251 children to intramuscular inoculation. The children, whose ages ranged from 2 months to 5 years, were divided into five groups so that several types and schedules of vaccination could be tried. The response was assessed by means of a virus neutralization test that measured the ability of the patient's serum, when mixed with virus, to prevent infection of a tissue culture by the virus. Three types of virus were used in this test.*

The resulting titers indicated that in general a single injection of vaccine did not evoke a demonstrable increase of neutralizing antibodies but that two injections did. Children receiving three injections responded with increased neutralizing antibodies for all three types of virus. In four groups, secondary inoculations were tried six months later and had a marked effect in increasing the antibody titer. Both infants and preschool children responded well to these vaccinations.

The demonstration of the effectiveness of poliomyelitis vaccine during the field trial of 1954 [1] was based upon controlled studies conducted among school children of the first, second, and third grades in which the vaccine was administered on a strictly defined schedule of three inoculations. Following the recommendation of Salk,[2] the dosage schedule was reduced during 1955 to two inoculations to be followed by a secondary stimulus approximately six months later. Confirmatory serologic evidence of the effectiveness of this dosage has been obtained by one of us (G.C.B.).[3] Although the range in age of children receiving vaccine was extended greatly during 1955, little information has been obtained with respect to the serologic response in different age groups except for some data concerned with the age range 1-5.[4] Since most immunization programs are inaugurated during the early months of life, the importance of information pertaining to the response of infants to poliomyelitis vaccine is evident. It is our purpose to report herein studies concerned with the serologic response of infants and preschool children to poliomyelitis vaccine under varying schedules of inoculation.

Plan of Study

The children who participated in this study were selected on a voluntary basis from about 450 children attending the University of Michigan Child Health Conference. Prior to the inclusion of each child in the study, written consent was obtained from one of the parents.

Vaccines Employed.—The poliomyelitis vaccines used in this study were commercially prepared by companies furnishing material in the field trial. The four lots of vaccine used had successfully passed certain minimum standards of antigenicity in monkey tests prior to being released for use in the field. Many of the infants received inoculations of "triple" vaccine (diphtheria toxoid, tetanus toxoid, and pertussis vaccine) manufactured and provided by the Michigan State Health Department concurrently with the poliomyelitis vaccine.

Immunization Schedules.—The 251 children in the study are classified in five different groups according to the type of vaccine received and the inoculation schedule. They are further divided into infants (from 2 to 12 months of age) and preschool children (from 1 to 5 years of age). Group 1 received three 1-ml. doses, Cutter E5721 vaccine; group 2 three 1-ml. doses, Wyeth 23401 vaccine; group 3 two 1-ml. doses, Wyeth 23401 vaccine; group 4 one 1-ml. dose, Wyeth 23401 vaccine; and group 5 three 1-ml. doses, Lilly 309 vaccine. (A small control group of unvaccinated children was included with group 5.) Second and third doses of vaccine were given

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Three of the lots of vaccine used in this study (Lilly 309, Cutter E5721, and Wyeth 23401) were graciously supplied by Dr. Jonas E. Salk of the University of Pittsburgh and represented lots used by him in children in Pennsylvania. Pitman-Moore 175 E008 vaccine was made available through the auspices of the National Foundation for Infantile Paralysis.

at intervals of one month followed by a reinforcing dose six months after the initial injection. All inoculations of vaccine were given intramuscularly in the upper, outer quadrant of the buttock.

Measurement of Serologic Response.—Venous blood samples were obtained from either the median cubital or the external jugular vein on the day of the first inoculation of vaccine. Postvaccination blood specimens were taken two to four weeks after the reinforcing dose. Throughout the greater part of the study, venous blood specimens were also secured from the mothers in order that their antibody titers might be compared with those of their infants.

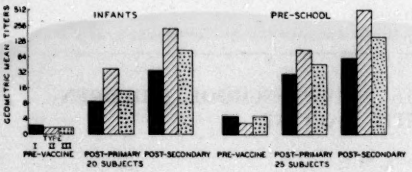

Fig. 1.—Antibody response of children in group 1 to primary and secondary vaccination.

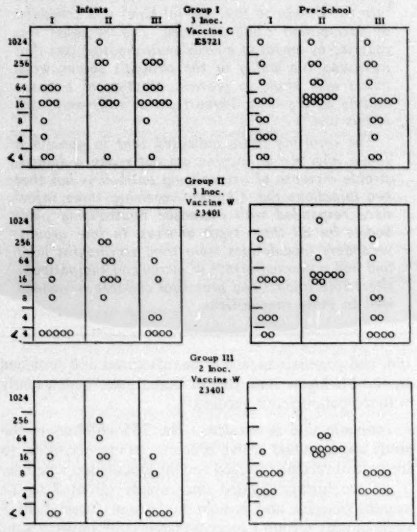

Fig. 2.—Antibody response in children with no demonstrable antibodies to any type virus before primary vaccination with antigenically good vaccine.

Virus neutralization tests were performed in tissue cultures of HeLa cells with the same basic materials and techniques used by this laboratory for specimens obtained during the field trial of 1954,[5] except that in the present study all virus-serum mixtures were preincubated before testing. The serums had been preserved at 4 C until tested. Original dilutions of 1:4, 1:8, 1:16, 1:64, 1:256, and 1:1,024 were mixed with equal quantities of three immunologic types of virus diluted to represent 100 tissue culture doses in the final inoculum. After incubation for one hour at room temperature, 0.5 ml. of each virus-serum mixture was added to stationary tubes of HeLa cells containing 0.25 ml. of maintenance solution. Appropriate virus titration and tissue and type specific serum controls accompanied each test. The tubes were incubated at 37 C and beginning at three days were examined under the microscope for the cytopathogenic effect of the virus. The highest dilution of serum completely protecting against virus activity was taken as the neutralizing titer.

Some of the paired serums from infants receiving both poliomyelitis and the "triple" vaccine are being tested as part of a separate study for pertussis antibody response that is being conducted with Dr. Pearl Kendrick of the department of epidemiology.

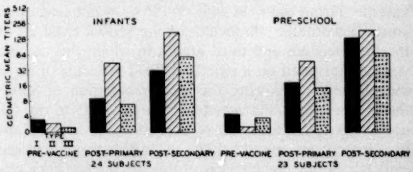

Fig. 3.—Antibody response of children in group 2 to primary and secondary vaccination.

Results

The parents of all children in the study were specifically requested to note and report any untoward reactions manifested by the children subsequent to the administration of the poliomyelitis vaccine. Throughout the study no such reactions were observed.

Group 1.—The 20 infants and 25 preschool children in group 1 received three injections of Cutter vaccine E5721. Reinoculation with the same vaccine was carried out six months after the first injection. Figure 1 presents the geometric mean antibody titers for the three types of virus. The data show clearly that there was an increase in mean antibody titer to each type of virus after primary vaccination, with a further rise subsequent to the reinforcing dose, and that the infants responded almost as well as did the preschool children. The response of those children having no demonstrable antibodies to any type before primary vaccination is shown in the top portion of figure 2. It will be seen that, although the titers are not all high, most are in the range generally believed to be significant.

Group 2.—Group 2 consisted of 24 infants and 23 preschool children. The children in this group and in groups 3 and 4 received the same vaccine, Wyeth 23401, but on different primary inoculation schedules, namely, three, two, and one injection respectively. Intervals were one month. All received secondary inoculations of the same material six months after the first injection. The pre and

postvaccination blood specimens of 24 infants and 23 preschool children in group 2 have been tested; their geometric mean antibody titers are shown in figure 3. The titers after primary vaccination indicate a good immunologic response in most of the subjects, infants as well as preschool children, which appears to be remarkably similar to that seen in group 1 children, who also received three injections but of a different vaccine. In children of both groups, the secondary vaccination resulted in a booster effect upon the antibody titers. The responses of

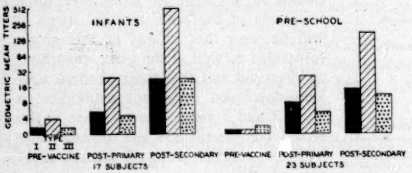

Fig. 4.—Antibody response of children in group 3 to primary and secondary vaccination.

children of this group having no demonstrable antibodies to any virus type before primary vaccination are shown in the middle portion of figure 2.

In addition to comparing the responses to the two different vaccines in human subjects, it was thought advisable to compare them by antigenicity tests in guinea pigs. Consequently, two groups of five guinea pigs each were inoculated three times at an interval of one week with 0.5 ml. of the Cutter and Wyeth vaccines used in children. The animals were bled two weeks after the third injection and neutralization tests performed with their serums. The titers obtained, although subject to slight individual variation, showed that both vaccines contained antigenically active components for all types and that the Cutter vaccine stimulated slightly higher titers to types 2 and 3 virus.

Group 3.—The 17 infants and 23 preschool children in group 3 received only two injections of Wyeth vaccine at an interval of one month as their primary vaccination. The geometric mean antibody levels of the 17 infants and 23 preschool children are shown in figure 4, where it will be seen that the mean titers after primary vaccination were not as high as in the groups receiving three injections. The response of those without antibodies to any type of virus, however, as shown in the lower portion of figure 2, indicates a satisfactory reaction. The response to the six-month inoculation in children of this group was generally not as great to types 1 and 3 as in the previous two groups, but the levels attained following this stimulus were satisfactory and the type 2 response in the infants was the highest level reached by any group in the study.

Group 4.—Group 4 consisted of 13 infants from 3 to 9 months of age. This small but interesting group received one inoculation of Wyeth vaccine as a primary stimulus. With one exception, all were devoid of antibodies before injection. Only a few developed low level antibodies, mostly to type 2 virus, after the single inoculation, which is obviously not sufficient stimulus for this age group. However, the reinoculation of these children six months later resulted in definite increases of antibody. The results with this group are shown in figure 5, where it will be seen that, although not of the same magnitude as in previous groups, the geometric mean antibody levels indicate that these children had developed an appreciable immunity.

Group 5.—The 61 infants and 45 preschool children in group 5, the largest group, received three inoculations of Lilly vaccine, lot 309, given at monthly intervals beginning in the fall of 1954. This particular lot of vaccine had, in fact, been used in some areas for the nationwide field trial earlier in the year but only as a third dose in conjunction with other lots. It had also been used early in the summer in separate studies,[3] in which good serologic responses were obtained in children ranging in age from 1 to 12 years. Unfortunately, this vaccine had been preserved with merthiolate and, by the time most of the children in our group had received their initial series of injections, the vaccine had apparently lost some of its antigenicity as judged by the lack of serologic response. The deterioration of vaccine after such exposure to merthiolate has been discussed at length by Salk,[2] and the progressive loss of antigenicity of lot 309 in tests with monkeys and in humans is adequately documented. Consequently, with few exceptions, the children in this group did not respond to this vaccine with the development of neutralizing antibodies. The almost complete lack of stimulus was unrelated to the presence or absence of demonstrable antibodies prior to the course of inoculations. The few children who had received an intended booster inoculation with ineffective material still failed to show an immunologic response. The majority of these children, however, received a potent vaccine for their secondary inoculation and responded quite well to this later stimulus. The secondary injection in most cases was completed with Cutter E5721 vaccine.

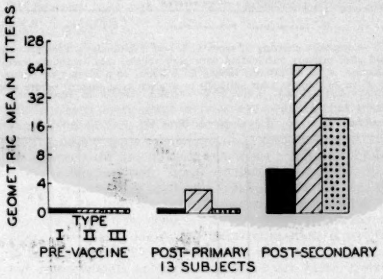

Fig. 5.—Antibody response of children in group 4 to primary and secondary vaccination.

Figure 6 shows the antibody status of the infants in this group at three periods: before and after primary vaccination and after the six-month injection. The data are arranged as a composite of the three separate types of antibody, and it will be seen that 44 infants prior to vaccination were lacking in demonstrable antibodies to one, two, or all three types of virus, totaling 107 such instances. The poor antigenicity of this lot of vaccine is evident. On the other hand, the booster effect of the secondary vaccination upon the development of antibodies

is marked. It is of interest, however, that no appreciable increase in titer was observed in those having antibodies prior to vaccination. The explanation for this is not clear.

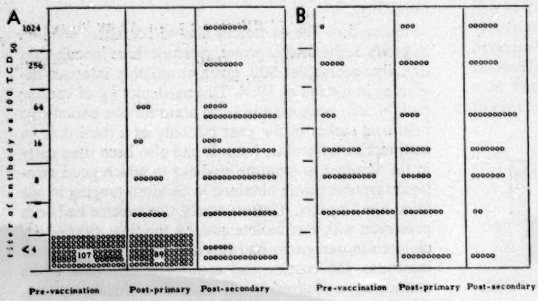

Fig. 6.—Composite charting of types 1, 2, and 3 antibody in infants of group 5 before and after primary vaccination with poor vaccine and secondary vaccination with satisfactory vaccine. *A*, in 44 subjects having no antibody to a given type before primary vaccination and, *B*, in 26 subjects with antibody to a given type present before primary vaccination.

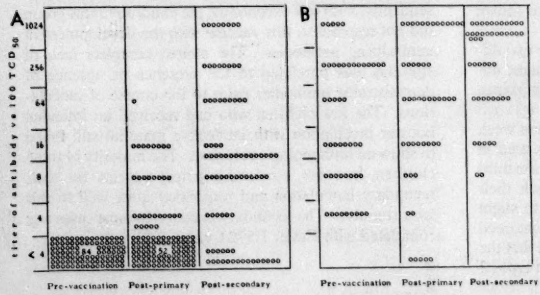

Fig. 7.—Composite charting of types 1, 2, and 3 antibody in preschool children of group 5 before and after primary vaccination with poor vaccine and secondary vaccination with satisfactory vaccine. *A*, in 39 subjects having no antibody to a given type before primary vaccination and, *B*, in 30 subjects with antibody to a given type present before primary vaccination.

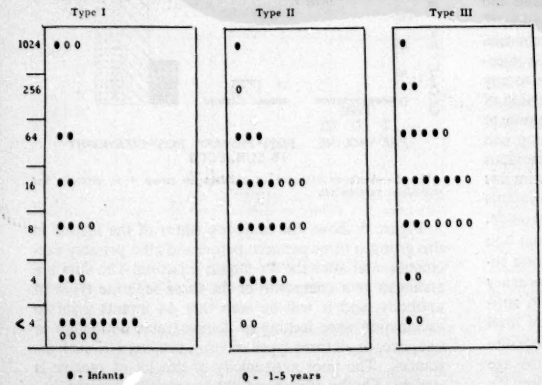

Fig. 8.—Effect of secondary inoculation in children of group 5 having no demonstrable antibodies after three injections of poor vaccine.

Figure 7 shows that the age group 1-5 responded in almost exactly the same manner, although children of this age group who possessed actively acquired antibodies before vaccination appeared to respond better than infants with passive antibodies.

Figure 8 is particularly significant in that it presents the effects of the six-month inoculation of potent vaccine in the children having no demonstrable antibodies to any type of virus after three injections of the poor vaccine. Again it will be seen that infants of this group responded as well as the older, preschool children did and that most of these subjects developed significant antibodies to types 2 and 3 virus. The response to the type 1 component was less marked; only half the children showed demonstrable antibodies.

Group 5 Controls.—There were 11 infants and 16 preschool children in a small group of children serving as nonvaccinated controls included in group 5. Venous blood specimens were secured from these 27 children at the same intervals as in the others in group 5, while during this period no vaccine was given. Three of these children showed an increase in type 3 antibodies and one of them an increase in type 2 antibodies. These are presumably natural exposures. All others remained without change during the period of study. Subsequent vaccination of these children resulted in a good response to all three antigenic components.

Mothers.— Neutralization tests have been completed on the serums of some of the mothers whose infants were vaccinated. These preliminary observations suggest strongly that, even when high titers of antibody are present in the mother's blood, passively transmitted antibodies are demonstrable in low titer in their infants' serum for three to four months only and that by the age of 5 to 6 months such antibodies could rarely be detected by present techniques. This portion of the study will be completed in the near future and additional information obtained with respect to the influence of passively and actively acquired antibodies on the response to poliomyelitis vaccine.

Comment

The need for information pertaining to the effectiveness of poliomyelitis vaccination of infants and preschool children has been greatly intensified by the recent demonstration of the protective action of the vaccine in school-age children. This study supplies serologic data of the response of these younger age groups to

the vaccine. The variation of dosage schedules for primary vaccination in the present study has furnished valuable information to those considering immunization of younger age groups. There seems to be little doubt that three inoculations evoke a satisfactory response in both infants and children aged 1 to 5 years. Two inoculations appear to be less effective and one injection in infants must be considered as definitely inadequate.

Physicians will be particularly interested in the serologic responses shown by infants 6 months of age and younger, since it is during this age period that most immunization programs are inaugurated. That these younger infants respond to poliomyelitis vaccine in a satisfactory manner is shown in the table, which compares their geometric mean antibody titers before and after vaccination with those of older infants.

The secondary inoculation with antigenic vaccine six months after the first injection served as a booster in all groups and was noticeably effective in those children receiving only one or two doses during their primary experience. This booster effect is in keeping with that found in previous studies with other age groups,[6] and, in the case of the group 4 infants who had received but one inoculation six months before, the effect is directly comparable to studies in progress at the present time with children in the Ann Arbor Schools whose second injection was delayed six months due to shortage of vaccine.[7] Preliminary results of these tests show a better response after delayed second inoculation than when the two doses were given a few weeks apart. The encouraging conclusion from data in the present study is that secondary inoculation with a good vaccine provokes as good an immunologic response in infants as in preschool children, even when the primary stimulus was apparently ineffective due either to inadequate dosage or to nonantigenic material. The data further suggest that, even though no demonstrable antibodies could be detected following a "poor" vaccine, there may have been a low level reaction to the original material that conditioned the subjects to subsequent stimulation.

Mean Antibody Titers of Infants

Primary Dosage, No. of Inoculations	Age, Mo.	Prevaccine Type 1	Prevaccine Type 2	Prevaccine Type 3	Type After Primary Vaccination 1	Type After Primary Vaccination 2	Type After Primary Vaccination 3	Type After Secondary Vaccination 1	Type After Secondary Vaccination 2	Type After Secondary Vaccination 3
3.....	2-6	<4	<4	<4	8	32	10	24	122	70
	7-11	<4	<4	<4	12	54	10	64	435	58
2.....	2-6	4	<4	<4	5	27	5	26	384	26
	7-11	<4	6	<4	6	19	4	19	256	16

The practicing physician will raise an obvious question of the comparison of the responses of infants and preschool children with those of school children in which the actual benefits in preventing clinical disease have been adequately demonstrated. A comparison of the present antibody titers with those of older, school-age vaccinated children who were tested in this laboratory as part of other studies has indicated that the serologic responses are essentially of the same magnitude.

Summary and Conclusions

In a study of the antibody response of 135 infants and 116 preschool children to poliomyelitis vaccine, four of five groups of children received potent vaccines on different primary immunization schedules. In two groups receiving three injections of different vaccines at monthly intervals, the majority of infants, including those 6 months of age and under as well as the children of preschool age, responded with increased neutralizing antibodies to all three types of virus. In another group of children who received two injections, the titers after the primary vaccination were not as high as in those receiving three inoculations. A group of infants receiving only one injection did not respond with demonstrable neutralizing antibodies. The effect of secondary inoculation six months later on all of these four groups was marked, and even those not responding well to primary vaccination showed appreciable development of antibodies. One group of children had unintentionally received three inoculations of a weakened vaccine and showed very little response to the primary stimulus, but good antibody production was observed following a secondary inoculation with a good preparation. This study indicates that infants and preschool children respond well to poliomyelitis vaccination and that the vaccine should be effective in these age groups.

109 Observatory St. (Dr. Brown).

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Treatment of Peptic Ulcer.—The ideal therapeutic agent [for peptic ulcers] must effect more-or-less complete but reversible elimination of free HCl, at doses which are well below toxic limits, and the mode of administration must be oral. Acetazoleamide meets the first of these conditions amply and the second only moderately well, since no disturbing side-effects were elicited provided the dosage was kept below 100 mg./kg. It does not meet the third condition, however, since the oral dosage required to attain the same blood level of the drug as that which effects 95% inhibition by the intravenous route is so great as to be impractical. This last deficiency rules out acetazoleamide, but new carbonic anhydrase inhibitors are being synthesized today which possess physical and chemical characteristics differentiating them markedly from acetazoleamide itself, and it is our hope that some new compound of this kind may satisfy all of the specifications for the ideal ulcer therapy. In the meanwhile, efforts to acquire insight into the fundamental chemical process of the parietal cell continue, and we are still hopeful that one day substances will be found which operate specifically against the enzyme systems of the canalicular wall. Such substances, being specific in their action on the parietal cell, will not disturb enzymatic processes in other tissues of the body, and thus they may likewise satisfy the clinical requirements for the ideal ulcer therapy—perhaps even more efficiently than inhibitors of carbonic anhydrase action.—Franklin Hollander, Ph.D., and H. D. Janowitz, M.D., Suppression of Gastric Hydrochloric Acid Secretion by Enzyme Inhibitors, *A. M. A. Archives of Internal Medicine*, February, 1956.

THE EARLY MANAGEMENT OF MYOCARDIAL INFARCTION

Col. Byron E. Pollock (MC), U. S. Army

• *The patient in the acute stage of myocardial infarction generally needs rest, reassurance, and relief from pain. Morphine is the preferred agent; it may be given by various routes and in doses of from 15 to 30 mg. Depending on conditions, the patient may also need hospitalization, oxygen therapy (ordinarily in an oxygen tent with a flow of 9 to 10 liters per minute), anticoagulant therapy (e. g., with warfarin sodium), coronary vasodilators such as papaverine, special nursing care, and particular attention to diet and elimination.*

After the acute stage, it may be necessary to treat complications such as shock, congestive heart failure, acute failure of the left side of the heart, pericarditis, and certain arrhythmias. Pressor drugs like mephentermine and levarterenol have improved the outlook of the patient in shock. Inflation and deflation of four sphygmomanometer cuffs may be carried out in clockwise order on the four extremities to relieve pulmonary edema.

During the recovery period, attention must be given to the gradual discontinuance of medication, the establishment of favorable personal and environmental attitudes, and the gradual resumption of physical activity.

The clinical picture in myocardial infarction is quite variable. Manifestations may vary from mild nausea or weakness to excruciating substernal pain with shock and collapse. The measures to be taken in management will depend upon the condition of each individual patient and cannot be reduced to routine. There are, however, important principles that can guide one in treatment, and the complications that may arise have their own therapeutic requirements to be considered. Several phases of management are more or less controversial at this time; in considering them I shall attempt to point out the difference in opinion and to indicate the viewpoint at which I have arrived from my own experience.

Early management of acute myocardial infarction does not begin with a confirmed diagnosis, but rather when the physician first suspects the possibility of this condition in his patient. The diagnosis must be made initially on clinical grounds, based on the patient's history, the character and location of pain and its duration, associated apprehension, pallor, shock, and possibly other findings. An electrocardiogram and other laboratory tests can be deferred until the patient is comfortable and in bed. In my opinion the rushing of a patient suspected of infarction to an electrocardiography laboratory is rarely defensible.

Management of the Acute Attack

Relief of Pain.—Relief of pain and reduction in the anxiety and fear of death that most patients experience are of first importance. Morphine is the preferred agent for these purposes, because of its ability to induce euphoria. The initial dose may well be given intravenously in order to secure its effect at once. Administration should be quite slow, so that it may be discontinued as soon as the pain is relieved. The dosage required will ordinarily be about 15 mg. (¼ grain), but as much as 30 mg. (½ grain) may be needed in the unusual case. For the patient whose pain and apprehension are not marked, intramuscular or subcutaneous administration of 15 mg. of morphine may suffice. Dihydromorphinone (Dilaudid) hydrochloride, 3 mg. (1/20 grain), or Pantopon (total alkaloids of opium as soluble hydrochlorides), 20 mg., are preferred to morphine by some, on the basis that they may less often cause nausea and vomiting. I consider meperidine (Demerol) hydrochloride inferior to morphine for the initial dose, because it has less euphoric action.

Rest.—Since the first report of Herrick on sudden obstruction of the coronary arteries,[1] the importance of rest has been recognized. The matter of rest, however, requires judicious analysis. During the period of softening and removal of the infarcted area and the early replacement with fibrous tissue, the heart must, of course, continue its pumping function. It is desirable that the heart beat with the least speed and force necessary to maintain vital function during this period. Physical activity predisposes to cardiac dilatation, cardiac rupture, cardiac aneurysm formation,[2] and to the development of important arrhythmias (including ventricular fibrillation). The patient should be put to bed in a comfortable position and should be given good nursing care to maintain comfort. The position need not be flat unless shock is present. Minor movements of hands and feet probably should be permitted to avoid discomfort and reduce peripheral stagnation of blood, which favors venous thrombosis.

Reassurance.—Reassurance of the patient is quite important at as early a time as possible. A "heart attack" often connotes death or invalidism, retirement, or the end of business and sexual life. It should be explained that the great majority of patients make a good recovery and resume productive work.

Home or Hospital Treatment.—The decision as to home or hospital treatment during the illness will depend on circumstances in each case. The condition of the patient and the distance to the hospital are probably paramount factors. When early shock, congestive failure, or arrhythmias are present, the superior facilities and nursing care available in the hospital should make it preferable. Certainly oxygen therapy and anticoagulant management are facilitated. Adequacy of the home for proper care, including freedom from annoyance and ease of availability of medical and nursing attention, will also play a role. Movement to the hospital should ordinarily

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Read before a Symposium on Common Diseases of the Cardiovascular System, New Jersey Academy of General Practice and American College of Angiology, Trenton, N. J., Feb. 19, 1956.

be made by ambulance, and the patient so handled as to minimize his activity during the trip and the preparation therefor.

Oxygen Therapy.—The use of oxygen in myocardial infarction is no longer a desperate or heroic measure. The principle of rest for the heart would require that oxygen be used for the patient who is cyanotic, dyspneic, in shock, in pulmonary congestion or edema, or suffering from a cardiac arrhythmia with rapid heart action. Persisting pain of myocardial infarction may be relieved or reduced by oxygen therapy. In other cases use of oxygen may well be justified for the first day or two, in an attempt to prevent gross anoxia and to compensate for less overt degrees of oxygen deficiency. It is my practice to use oxygen therapy in all but the mildest cases if they are seen early after the infarction. The use of an oxygen tent is ordinarily the most acceptable method of administration. Oxygen is provided at about 9 to 10 liters per minute; temperature in the tent is maintained at a level of comfort for the patient, usually 60 to 68 F. The occasional patient who is apprehensive in an oxygen tent may be given oxygen by face mask or face tent. Oxygen therapy may usually be discontinued after one to three or four days of use when the evidence of anoxia has ceased to exist. A method often used is to remove the tent for a few daytime hours at first, allowing the patient to sleep in the tent at night. The following day the tent is left off unless indications for its use reappear.

Anticoagulant Therapy.—The question of anticoagulant therapy arises early. The theoretical value of anticoagulant therapy is in prevention of extension of the coronary thrombus, prevention of embolism from a mural thrombus in the left ventricle, and prevention of thrombosis in the venous system and right side of the heart with subsequent pulmonary embolism. The results of the study by the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction are impressive. In a series of 1,031 cases, Wright [3] reports that the mortality was 23.4% in patients not receiving anticoagulant therapy as compared with 16.0% in the patients receiving anticoagulants. In 26 of each 100 control patients, 41.8 embolic complications occurred, whereas 13.1 embolic complications developed in 10.9 of each 100 under anticoagulant therapy. The greatest benefit of anticoagulant therapy appeared in the elderly, in the patients having had previous infarction, and in patients with severest illness. Abundant confirmation, although not universal, of the value of anticoagulant therapy has subsequently appeared. Several serious students of anticoagulant therapy have proposed, however, that in the mild, "good risk" cases the mortality and morbidity is little different whether or not anticoagulant therapy is used. Certainly analyses made in retrospect support this view. A point of contention at this time is whether one can decide on the first day of illness whether the patient with myocardial infarction will continue to follow a mild course. In my view and that of others,[4] one cannot often make that decision with confidence in the individual case.

Contraindications to anticoagulant therapy include lack of a dependable laboratory and presence of hemophilia, hepatic disease with low prothrombin level on initial test, lesions of brain or spinal cord, and recent ulceration of the gastrointestinal tract. Decision to treat the patient at home may make anticoagulant therapy more difficult but may not prevent its successful use.

For several years bishydroxycoumarin (Dicumarol) has been the agent most widely used in anticoagulant therapy. It acts by lowering the prothrombin level of the blood, probably through reducing its production by the liver. A period of 48 to 72 hours is required from the time of initiation of therapy until a therapeutic hypoprothrombinemia of 10 to 30% of normal is obtained. This corresponds roughly with prolongation of prothrombin time by two to two and one-half times. Usually an initial dosage of 300 mg. orally is required, followed by 100 to 200 mg. the following day. Two methods of follow-up therapy are in use: (1) the continuous method, which aims at giving almost daily dosage sufficient to maintain hypoprothrombinemia within the therapeutic range, and (2) the intermittent method, which involves the giving of a larger dose of bishydroxycoumarin at longer intervals to produce a series of swings of prothrombin level from just above the therapeutic range down to the lower levels and back up again. A clear advantage has not been proved for either method. Most physicians, including myself, use the continuous method. It should be held in mind that the day-to-day dosage will not reach full effect for about 48 hours, so that the prothrombin curve must be projected forward mentally to estimate the proper amount of the drug to administer.

In case of prolonged levels of hypoprothrombinemia below the therapeutic range, spontaneous bleeding may occur with manifestations such as microscopic hematuria, gross hematuria, epistaxis, and, in more severe and prolonged hypoprothrombinemia, intestinal bleeding and petechial hemorrhage. Fatalities have occurred. Since, however, the hypoprothrombinemia is reversible by the administration of vitamin K and its analogues, and more rapidly by vitamin K_1 or blood transfusion, it appears that significant hemorrhage should be avoidable and, if it occurs, quickly controllable.

Newer agents for obtaining therapeutic hypoprothrombinemia are ethyl biscoumacetate (Tromexan), cyclocumarol (Cumopyran), and phenindione and its derivatives. These agents act in a similar manner to bishydroxycoumarin, and their effects may be counteracted by vitamins K and K_1. All of them are administered by mouth. Ethyl biscoumacetate is rapid-acting, inducing therapeutic effect within 18 to 36 hours, but it maintains therapeutic effect for only a brief period of about 36 hours. This results in a rather fluctuating level of effect and makes control of maintenance dosage difficult. Cyclocumarol is effective in producing a therapeutic level in 24 to 36 hours, with effect lasting 4 to 14 days. It would appear to have some advantage in time of effect over bishydroxycoumarin. Phenindione and its derivatives have proved useful, producing therapeutic levels of hypoprothrombinemia in 24 to 36 hours. Effect is maintained over a period of several days. Side-reactions have been noted by some investigators,[5] however, that may detract from the drug's usefulness: albuminuria, allergic manifestations, and agranulocytosis.

During the past three years, my experience [6] has been almost wholly with a new drug of the coumarin group, warfarin (Coumadin) sodium, which I have now used in some 100 cases of myocardial infarction. This agent may be given either intravenously or orally, and an initial dose of approximately 75 mg. of the drug regularly produces a therapeutic level of hypoprothrombinemia within 20 to 24 hours, depending on the route of administration. It is long-acting, a single dose maintaining effect for four to six days. The maintenance dose by the continuous method, based on daily prothrombin determinations, varies in different individuals from 4 to 19 mg., averaging about 10 mg., and is consistent from day to day in the same patient, thus facilitating maintenance of a smooth level of hypoprothrombinemia. The prothrombin level is responsive to vitamin K analogues and to vitamin K_1. On several occasions a low prothrombin level has responded to very small doses of phytonadione (Mephyton) of the order of 2.5 to 5 mg., with elevation into the desired therapeutic range. No side-effects (other than the production of hypoprothrombinemia) were encountered. In my opinion, the properties of warfarin sodium make it more nearly an ideal anticoagulant than the other agents now available.

Heparin differs markedly from the anticoagulants just discussed. It does not act primarily as a hypoprothrombinemic agent but rather as an agent to prevent reaction of thrombin with fibrinogen to form a clot. When given intravenously it is rapidly effective (in a period of 10 minutes), but the effect wears off in four to six hours, so that repetition of dosage is necessary. A dose of 50 to 75 mg. every four hours or 75 to 100 mg. every six hours usually constitutes adequate anticoagulant therapy. Heparin may also be given in concentrated form into subcutaneous tissues or fat deposits, with dosage controlled by successive Lee-White clotting time determinations. This latter method has given variable and rather unpredictable results in my hands, and I, therefore, prefer the intravenous method. When heparin is given intravenously along with the initial dosage of warfarin sodium and repeated at six-hour intervals, it will usually be possible to discontinue the use of heparin after four doses, due to production of the therapeutic level of hypoprothrombinemia by the warfarin. Blood for the prothrombin test should not be drawn within four hours of heparin administration, because of some hypoprothrombinemic effect of heparin.

Coronary Vasodilators.—Several drugs have been advocated for use in the early treatment of patients with myocardial infarction with a view to improving coronary circulation through vessels that remain patent and relieving any element of coronary spasm. Experimental results on animals [7] indicated that papaverine was effective as a coronary dilator and, further, that it reduced cardiac irritability and the ease with which ventricular fibrillation was induced. Its use in dogs reduced the mortality resulting from ligation of a coronary artery. For these reasons, plus its mild sedative effect and freedom from constipating action and habituation, its clinical use in man was recommended. The drug may be used intravenously or intramuscularly in dosage of 65 to 100 mg. three or four times daily. If given orally, absorption is incomplete and the agent has a tendency to nauseate. Oral dosage of about 200 mg. three or four times daily is used. Convincing clinical evidence of benefit is frequently lacking, and in recent years the protagonists of papaverine have lost their earlier enthusiasm.[8] Aminophylline is sometimes used for coronary vasodilator effect, by slow intravenous administration of 0.25 to 0.5 gm. in solution. On occasion this measure is useful in relieving residual pain of the infarction. Subsequent dosage may be given intravenously at six-to-eight-hour intervals, or rectal suppositories containing 0.5 gm. of the drug may be used. Atropine sulfate, given subcutaneously in dosage of 0.4 to 0.8 mg. (1/150 to 1/80 grain), is sometimes recommended for the purpose of relaxing reflex-vagal coronary constriction. Clinical evidence of benefit is lacking. I have no strong feeling either for or against the use of these drugs.

Other Drugs.—Mild sedatives such as phenobarbital (30 mg. three times daily) and secobarbital (Seconal) (0.1 gm. given at bedtime) may contribute to rest and sleep. Penicillin and other antibiotics serve no useful purpose unless pneumonia or other infection intervenes. Cortisone should not be used; it offers no benefit and probably delays the removal of necrotic cells and initiation of the scar.[9]

Nursing Care.—Good nursing care is essential to proper management of the case of myocardial infarction. Much can be done to insure the patient's comfort, provide a cheerful atmosphere, give proper medication, supervise minor activity of extremities, bring the patient to feeding himself within a few days, and protect the patient from telephone calls and visits by tactless friends and business associates. Nursing care must not be so strict as to deny the patient minor movements, elevation of the head of the bed, and changes of body position with assistance. Laboratory tests, such as electrocardiograms, leukocyte and differential cell counts, erythrocyte sedimentation rate determinations, and prothrombin tests should be fitted into the patient's program so as not to interfere repeatedly with his rest. X-ray studies may often be deferred.

Diet.—Diet will consist of liquids for the first day or two, with attention to avoiding distention. Thereafter a diet of restricted caloric content low in fat and cholesterol is given, preferably broken into small feedings about five times daily. Overfeeding should be avoided, particularly in the patient who is already obese. Vitamin supplement may be provided. Coffee in small quantities may be allowed if it does not cause restlessness. Alcohol may be permitted in moderation if the patient desires it and if there are no contraindications. Tobacco should be prohibited during the acute illness and is probably best avoided thereafter.

Bowel Movements.—The patient should not be disturbed by insistence on bowel movement during the first two or three days. He is apt to be constipated because of the effect of morphine, lack of activity, and limited food intake. Mineral oil or milk of magnesia at night, assisted by a small saline enema in the morning, may initiate movements after the early period has passed and prevent

straining at the stool. Use of the bedpan usually presents a problem. In many patients a great amount of physical effort and mental stress results from attempts at its use. Lifting the patient carefully and with reassurance onto a bedside commode or a nearby bathroom commode is saving in cardiac effort and usually is considerably more acceptable.

Management of Complications

Shock.—Shock occurs in some 10% of cases of myocardial infarction; it is considered by some as part of the basic condition. The manifestations are similar to shock from other causes: the systolic blood pressure falls to 80 mm. Hg or below (100 mm. Hg in previously hypertensive patients), the pulse is fast and thready, the skin is cold and moist, and the patient shows a pallid cyanosis, faintness, stupor, or coma. A few years ago no effective treatment was available and a mortality rate of about 80% prevailed. Blood transfusion, venous or arterial, gave dramatic results in a few cases but on the whole was disappointing; excessive infusion led to pulmonary edema or congestive failure or both.

Pressor drugs recently brought into use have improved the outlook significantly. Mephentermine (Wyamine)[10] and levarterenol (Levophed)[11] are effective pressor agents. I have had no personal experience with metaraminal (Aramine),[12] which is also reported to be effective. Mephentermine may be given initially intravenously in dosage of 5 to 15 mg. and followed by intramuscular dosage of 20 to 30 mg. every one to two hours as needed. A steady, sustained pressor effect on blood pressure results in most cases. For more refractory patients, mephentermine may be given by continuous slow intravenous drip of a solution of 75 to 100 mg. of the drug in 100 cc. of 5% glucose in water. Levarterenol is probably a more potent pressor agent than mephentermine; I have seen cases in which mephentermine ceased to exert demonstrable effect, while change to levarterenol produced satisfactory blood pressure elevation. Levarterenol must be given in dilute solution (of 5% glucose in water) by intravenous drip. The pressor response varies immediately with the speed of the drip. Close supervision of the speed by a nurse or attendant at the bedside is necessary in order to avoid an excessive hypertensive response and yet to maintain blood pressure at the desired level of about 100 mm. Hg systolic in previously normotensive patients and about 120 mm. Hg in previously hypertensive patients. Pressor effect of either drug used should be maintained until a careful test of withdrawal demonstrates the patient's ability to maintain a satisfactory blood pressure without it. This may be a matter of hours to several days.

In the case of levarterenol the usual strength required is 4 mg. per liter of glucose solution, given intravenously at about 20 to 30 drops per minute. If a speed greater than 40 drops per minute is required, it is probably better to use a stronger preparation so as to reduce the volume of fluid administered. In practice, solutions varying from 2 to 32 mg. of the drug per liter of fluid have been used. When one discontinues the levarterenol drip, it is good practice to substitute a slow drip of 5% glucose solution, lest a hypotensive reaction recur requiring reinitiation of levarterenol therapy. Care should be taken to prevent extravasation of levarterenol solution into subcutaneous tissues. Tissue sloughs have resulted from this cause.

The duration of shock before initiation of treatment is important in determining the patient's response to the drug. Treatment should be initiated at the earliest possible moment without awaiting a possible spontaneous recovery of the patient from shock. Using mephentermine, Hellerstein and Brofman[10] reported recovery from shock of 14 out of 17 patients; 7 later died from the extent of their infarction, and 7 recovered. Sampson and Zipser,[11] who used levarterenol, reported recovery from shock of 20 out of 30 patients, 4 of whom later died of other causes while 16, or 53%, recovered. Experience of others is of a similar order.

Acute Failure of Left Side of the Heart.—Acute failure of left side of the heart, manifested by pulmonary edema, may result so promptly and directly as a result of the myocardial damage as to be considered a part of the infarction itself. Treatment of the same kind is given in these cases as in pulmonary edema from other causes. Immediate and at times rather drastic measures are necessary. The patient should be elevated to a sitting position in bed and morphine sulfate (30 mg.) should be given hypodermically or intravenously. Sphygmomanometer cuffs should be applied to the four extremities and inflated to the diastolic blood pressure level. One cuff left uninflated is rotated from limb to limb every 15 minutes, usually in a clockwise manner. Oxygen is best given by mask, preferably under positive pressure of about 10 mm. Hg. Alcohol (20 to 30% solution) introduced into the humidifier bottle of the oxygen apparatus may be helpful in reducing the foaming in pulmonary edema. Mercurial diuretics are often given, but it should be held in mind that they will hardly act fast enough to be of use during the immediate attack. Rapid digitalization is widely used with apparent clinical benefit attributed to effect in improving the output of the left ventricle; some objection is voiced to its use on the grounds that its failure to affect the damaged left ventricle while increasing the output of the right ventricle will make the pulmonary edema worse.[13] Aminophylline (0.5 gm. given slowly intravenously) is also widely used to relieve bronchospasm accompanying the attack. I have not seen any adverse effects and have the impression that, given with positive-pressure oxygen therapy, it may be quite effective. Use of this drug is strongly objected to by some, on the ground that bronchospasm is a protective mechanism designed to increase intra-alveolar pressure and combat pulmonary edema, and thus its abolition favors greater edema. These several measures usually prove adequate to overcome the attack of pulmonary edema.

A problem of recurrence of pulmonary edema occasionally arises when one attempts removal of the tourniquets. They should be removed one at a time at intervals of about 15 minutes. Should the patient's condition worsen upon their attempted removal, phlebotomy with removal of 500 to 600 cc. of blood should be considered.

Cardiac Arrhythmias.—Cardiac arrhythmias are common following myocardial infarction. Fortunately, most of them are benign and subject to good control. An occasional premature beat should not necessitate treatment. Frequent ventricular premature beats, especially if from multiple foci, require suppression with 0.2 to 0.6 gm. of quinidine given three or four times daily. Rapid atrial rhythms are detrimental, due to the associated rapid ventricular rate; digitalis is the drug of choice, since by causing or increasing atrioventricular block it slows the ventricular rate.

Paroxysmal ventricular tachycardia presents a special problem, in that it cannot be long sustained by the patient with myocardial infarction without fatal result. Drastic measures are justified if necessary to control this arrhythmia. If the general condition of the patient continues to be satisfactory, quinidine may be given orally at two-hour intervals in increasing dosage, of the order of 0.4 gm., 0.6 gm., 0.8 gm., to obtain conversion. If the patient's condition is deteriorating, parenteral medication is necessary. I prefer use of procainamide (Pronestyl) hydrochloride diluted in 5% glucose solution and administered intravenously so that the patient receives 50 to 100 mg. per minute. A direct-writing electrocardiograph is operated continuously during the procedure, so that administration of the drug may be stopped when the rhythm reverts to normal or in case the electrocardiogram should begin to worsen appreciably. The maximum intravenous dose to be given is 1 gm. An alternate method, particularly necessary if procainamide fails in conversion to normal rhythm, is the use of quinidine gluconate intramuscularly in dosage of 0.4 to 0.6 gm. every two hours. The intravenous use of quinidine preparations is fraught with hazard and should be considered only in extremis. In such a case, up to 0.6 gm. of the drug should be given very slowly, well-diluted, under electrocardiographic control. Significant hypotension or shock may result both from ventricular paroxysmal tachycardia and from the intravenous use of procainamide. Administration of pressor drugs, such as levarterenol, may be necessary to support blood pressure and may, as a result, facilitate the conversion of the arrhythmia.

Minor degrees of atrioventricular block, represented by prolongation of the P-R interval of the electrocardiogram or occasional dropped beats, should not require treatment but indicate caution in the use of digitalis. Fortunately, complete heart block with Stokes-Adams attacks is rare. Isoproterenol (Isuprel) hydrochloride is probably the drug of choice in preventing attacks in these cases. In the presence of complete heart block, the administration of quinidine and procainamide is dangerous because of their potentiality for suppressing completely cardiac impulse formation.

Congestive Heart Failure.—In congestive heart failure occurring after myocardial infarction, the usual treatment is given, consisting of a digitalis drug, a salt-poor diet, and diuretics as necessary. Care should be taken to avoid overdigitalization, since the myocardium is already irritable and ventricular tachycardia may be produced.[14]

Pericarditis.—Pericarditis involving a focal area about the infarct is a common occurrence in myocardial infarction and requires no special attention. A generalized pericarditis occasionally develops, manifested by a loud, rough, persistent pericardial friction rub and the occurrence of RS-T segment elevation in the electrocardiogram in leads taken over a wide area of the precordium. Pericardial effusion also may occur. A generalized pericarditis was not unknown in the preanticoagulant years,[15] but since the use of such drugs has become widespread it presents a new problem. Reports of hemorrhagic pericarditis occurring in patients under anticoagulant therapy suggest a causal relationship.[16] In one case of mine in which anticoagulant therapy was discontinued, the patient died a few days later from multiple arterial embolism. My present feeling is that anticoagulant therapy should be continued with care that low levels of prothrombin are not produced. Under such circumstances, one should be prepared to perform pericardiocentesis for the relief of cardiac tamponade if this should become necessary.

Other Complications.—A consideration of the management of pulmonary and peripheral embolism, while important, leads one too far afield from the subject of this discussion. The occurrence of a new myocardial infarction or extension of the present one requires a reassessment of the adequacy of anticoagulant therapy. The measures already discussed for the management of early myocardial infarction should be reapplied as necessary, and one should count the time elapsed from the new attack or extension rather than from the original infarction.

Further Care

After the patient has passed through the acute attack of myocardial infarction and the first few days fraught with the danger of complications, new questions begin to arise. These include the discontinuance of the early therapeutic measures, the problem of armchair rest versus bed rest, the reinitiation of mental occupation, and the gradual restoration of physical activity.

Discontinuance of Early Therapy.—When the substernal pain and dyspnea of the attack have gone, such drugs as morphine serve no useful purpose. Aminophylline or papaverine soon cease to be worth the disturbance caused the patient by their parenteral administration. Use of oxygen, as already noted, was discontinued after 24 to 48 hours in the patient who manifested no positive indication for its continuance, such as cyanosis, shock, pulmonary congestion, or serious arrhythmia. In patients with these latter conditions, oxygen therapy may be discontinued when the indication is no longer operative. The early intravenous administration of heparin has given way to use of the longer-acting agents after 24 to 72 hours, depending on the hypoprothrombinemic agents used.

Mental Calm.—Returning mental alertness of the patient will indicate the need for a factual and optimistic discussion of the nature of the patient's illness with his physician, including the reasons for advising a long period of rest and convalescence. Problems weighing on the patient's mind should be met with solutions so far as possible in order to increase the quality of subsequent rest.

This may necessitate brief visits by tactful business associates. The oversolicitous and annoying visitor should be avoided.

Armchair Rest.—After a few days to two weeks, depending on the seriousness of the illness, the patient will find bed rest to be tiring and tedious. Then, and with no contraindication of hypotension or excessive weakness, rest in a comfortable armchair may be begun. The key word to bed rest is rest and not the bed. Oftentimes periods of rest in an easy chair prove less arduous than unbroken time in bed. The patient must be lifted carefully into the chair and back into bed. Rest in a chair does not imply increased activity or early ambulation. The length of time spent sitting up should be short (about 15 minutes) to start with. It may be progressively lengthened according to the response of the patient, as shown in fatigue, pulse response, and blood pressure reaction.

Beginning Physical Activity.—During the third and fourth weeks, the patient is allowed increased movement of extremities in bed and while sitting, occupational therapy within his capability, and newspapers and magazines that he can manage himself. Letter-writing may be permitted. An increasing number of short visits with congenial friends may be in order. During the fifth and sixth weeks, standing leads progressively into walking on the level, and the beginning of stair climbing. The patient is no longer in the period of early management of myocardial infarction.

Summary

After occurrence of acute myocardial infarction, early avoidance of physical activity is combined with morphine administration for relief of pain. Oxygen administration and bed rest reduce cardiac demands. Coronary vasodilator drugs attempt better cardiac nutrition. Anticoagulants should be used in most cases to prevent extension of coronary thrombosis and embolism from mural thrombosis and phlebothrombosis; proper selection of the agent used may offer advantages.

Complications feared during the first few days after the acute infarction include medical shock, pulmonary edema, serious cardiac arrhythmias, extension of the area of infarction, embolism from mural thrombosis in the left ventricle, pericarditis, and congestive heart failure. Shock requires early recognition and institution of measures to maintain blood pressure. Prompt use of pressor drugs such as mephentermine (Wyamine) or levarterenol under good control may be lifesaving.

The onset of pulmonary edema requires prompt and vigorous therapy. Morphine administration to relieve apprehension, elevated position of upper part of body, trapping of blood in the extremities, and administration of oxygen by intermittent positive pressure along with use of an antifoaming agent usually lead to relief. Rapid digitalization and use of aminophylline may theoretically harm the patient in this condition, but practically they continue to be useful and sometimes essential measures.

Atrial arrhythmias producing rapid heart action demand reduction in heart rate, usually best achieved by digitalization. Ventricular irritability calls for administration of suppressive medication such as quinidine or procainamide, usually orally. Ventricular paroxysmal tachycardia produces severe cardiac and circulatory stress in the patient with an acute myocardial infarction and must be converted as promptly as possible. Careful slow intravenous injection of procainamide under electrocardiographic control is probably the method of choice; intramuscular use of appropriate quinidine preparations may be resorted to in case of failure of procainamide to convert the tachycardia to normal rhythm.

Adequate anticoagulant therapy is directed toward prevention of mural thrombosis in the left ventricle with subsequent embolism and peripheral venous thrombosis with embolism. Occurrence of significant pericarditis secondary to myocardial infarction was not unknown in the preanticoagulant era; bleeding into the pericardium may be enhanced by low prothrombin levels. Agreement is not present among cardiologists as to action required in such cases. In my opinion one should maintain prothrombin levels of 30 to 40% of normal and maintain watchfulness to note and relieve pericardial tamponade should it develop.

Congestive heart failure following myocardial infarction requires the usual treatment for such failure: digitalization, salt restriction, and the use of diuretic drugs. Combinations of complications gravely increase the prognosis and call for careful and adept combinations of therapy. This is particularly so when combinations of shock, ventricular arrhythmias, and pulmonary edema occur.

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TOXIC EFFECTS OF AMMONIUM CHLORIDE IN CARDIAC, RENAL AND HEPATIC DISEASE

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• *Ammonium chloride, administered by mouth in doses of 4 to 6 gm. per day, is valuable in preventing hypochloremic alkalosis and improving the diuretic response to mercurials. In four cases here described, however, it caused lethargy, air hunger, and other severe symptoms of intoxication.*

Three of the patients had long histories of heart disease. The fourth had a chronic infection of the urinary tract. In each there was reason to believe either that the liver failed to metabolize ammonium compounds normally or that the kidneys failed to excrete the products. In addition, ammonium chloride in sufficient dosage is capable of producing acidosis in normal subjects.

The acidosis can be combated with suitable alkalies such as sodium lactate, but the hepatic coma is not influenced by any specific therapy. It is therefore necessary to determine a patient's renal and hepatic status before instituting ammonium chloride therapy.

Ammonium chloride is often included in the therapeutic regimen of congestive heart failure. It is less frequently used in the treatment of hepatic cirrhosis with edema or as an acidifying agent in certain renal tract infections. That this drug may produce severe metabolic acidosis or other toxic effects in patients with these conditions is not always appreciated. An adverse course is often attributed to the underlying disease process rather than to the treatment. It is, therefore, problematical how often ammonium chloride is a factor in producing deleterious effects or in furthering serious electrolyte disturbances. But it may very well be a frequent occurrence, since the drug is widely used in home and hospital practice, often without the guidance of serum electrolyte determinations.

This study presents illustrative case reports that demonstrate the manner in which patients may be adversely affected by ammonium chloride. Contraindications to the use of this drug and the need for close observation and periodic electrolyte determinations during its administration are stressed. The following four cases were observed within a one-year period.

Report of Cases

CASE 1.—A 49-year-old woman was admitted to the hospital on April 16, 1953, because of increasing dyspnea, fatigue, and peripheral edema. A diagnosis of rheumatic heart disease had been made when she was 23 years of age, after the development of exertional dyspnea and ankle edema. With limitation of activity, she did well until she was 44 years of age, when her dyspnea and peripheral edema increased and she was placed on digitalis therapy. Subsequently, she was hospitalized several times for control of congestive heart failure. For two years preceding the present hospital admission, she had been on a regimen of occasional parenterally given doses of mercurial diuretics and a salt-restricted diet. Two weeks prior to hospitalization, she began to feel very tired, her dyspnea increased, and her appetite became poor. With meralluride (Mercuhydrin) sodium injections she lost 10 lb. (4.5 kg.) in weight, but her condition became worse. She was dyspneic and cyanotic even on minimal exertion.

On physical examination of the patient, temperature was 97 F (36.1 C), pulse rate 120 per minute (irregular), respiration rate 28 per minute, and blood pressure 105/75 mm. Hg. She was alert, moderately well nourished, and somewhat dyspneic. The sitting position was the most comfortable. There were numerous moist rales heard over the lower fields of both lungs with dulness to percussion and suppressed breath sounds over the base of the right lung posteriorly. The left border of cardiac dulness extended to the anterior axillary line. There was a prolonged grade 2 apical diastolic rumble without a systolic murmur. A slightly tender liver was palpated 4 cm. below the right costal margin. There was mild pitting edema of the right ankle. On x-ray and fluoroscopic examination of the chest, generalized cardiac enlargement with a large left atrium and conus arteriosus and evidence of pleural effusion on the right side were observed. An electrocardiogram showed auricular flutter with a changing degree of auriculoventricular block, the ventricular rate being about 174 per minute. The serum nonprotein nitrogen level was 30 mg. per 100 cc., carbon dioxide–combining power 43 vol. %, and chloride level 108 mEq. per liter. On urine examination, the specimen had an acid reaction, with a specific gravity of 1.015; it contained 4+ albumin. There were 10 to 15 white blood cells per high-power field, and the Benedict test for sugar was negative.

Course.—On admission the patient was in moderately severe failure of the right side of the heart. This was thought due to progressive mitral valvular deformity, although superimposed pulmonary infection, active rheumatic fever, subacute bacterial endocarditis, and suddenly developing arrhythmia were also considered as possible precipitating factors. The patient was placed in an oxygen tent and given meralluride intramuscularly, and her usual dosage of digitalis was increased. On this treatment she then improved, and the heart rate slowed to 80 to 90 per minute. On the third hospital day ammonium chloride administered orally, 1 gm. four times a day, was added to the regimen in an effort to increase diuresis. The following day her condition was worse. She was apathetic and more dyspneic, with rapid, shallow respirations. All food and liquids were refused, and oliguria occurred. Her lethargy increased, and she became drowsy. After three days of ammonium chloride therapy, the serum nonprotein nitrogen level was 84 mg. per 100 cc., carbon dioxide–combining power 34 vol. %, and serum chloride level 94 mEq. per liter. Therapy with the drug was discontinued, and she was given 5% sodium chloride solution and, later, M/6 sodium lactate solution intravenously. The blood levels of serum electrolytes improved, as shown in figure 1, and her lethargy and drowsiness gradually disappeared. Five months later she underwent mitral valvulotomy with excellent results.

This patient was admitted to the hospital in severe congestive heart failure. Response to bed rest, administration of mercurial diuretics, and increased dosage of digitalis was good. However, after administration of ammonium chloride for purposes of hastening her recovery, an electrolyte abnormality developed along with clinical evidence of severe acidosis. The prompt appear-

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ance of acidosis with the use of this drug and the gradual recovery following its withdrawal strongly implicate ammonium chloride as the precipitating factor.

CASE 2.—A 76-year-old female was hospitalized because of chronic cardiac insufficiency due to aortic regurgitation, presumably the result of rheumatic heart disease. For many months her congestive failure had been fairly well controlled by a salt-restricted diet and occasional injections of meralluride. Because of persistent pulmonary basil rales, on March 14, 1953, ammonium chloride, 4 gm. daily, was added to the regimen to potentiate the effects of the mercurial diuretic. At that time she was quite comfortable, except for occasional brief episodes of shortness of breath while at rest. She was a small, thin, mentally alert elderly woman. On physical examination, a few moist rales were heard at the bases of both lungs. The left border of cardiac dulness extended to the anterior axillary line. There were grade 3 systolic and diastolic murmurs at the right cardiac base, which were widely transmitted over the precordium. Blood pressure was 180/90 mm. Hg. The liver was not palpable. There was no ascites or peripheral edema. X-ray and fluoroscopic examination of the chest showed a greatly enlarged left ventricle, a tortuous aorta, and slightly increased hilar markings.

An electrocardiogram revealed low T waves in limb lead 1 and a ventricular rate of 72 contractions per minute, with frequent premature ventricular contractions. The hemoglobin level was 11 gm. per 100 cc., hematocrit 36%, and white blood cell count 9,000 per cubic millimeter. In numerous urine examinations, the specific gravity varied, being between 1.002 and 1.013, and albumin ranged from a trace to 2+. Tests for sugar were negative, but microscopic examination revealed from 2 to 50 white blood cells per high-power field and occasional hyaline and granular casts. A urine culture yielded only hemolytic micrococci (staphylococci).

Course.—After one day of ammonium chloride therapy, the pulmonary basilar rales were not heard. She continued to feel well until the seventh day of administration of ammonium chloride, when she was lethargic and anorectic. During the next four days she was acutely ill. She was drowsy and at times disoriented. She complained of weakness, thirst, and anorexia and said she saw red spots before her eyes. Physical examination revealed no significant change. Urinary output was not diminished. Ammonium chloride therapy was discontinued on March 21, after seven days' administration. She was then given 200 cc. of 5% sodium chloride solution intravenously because low-salt syndrome was suspected. Her status remained unchanged, however. Two days later the serum carbon dioxide–combining power was 18 vol. %, the nonprotein nitrogen level 124 mg. per 100 cc., and serum chloride level 118 mEq. per liter. Urine pH was 4.5. Oral administration of sodium bicarbonate was instituted and fluid intake maintained by a 5% solution of dextrose in water given intravenously. During the next few days, she gradually returned to her previous status clinically, and her serum electrolytes were restored to previous levels. Six weeks later, a phenolsulfonphthalein test revealed only a 5% excretion of dye in two hours. Other laboratory values are shown in figure 2.

Ammonium chloride was administered to this patient in spite of the fact that the nonprotein nitrogen level had been moderately elevated on several previous instances. Although this patient's symptoms were at first attributed to low-salt syndrome on clinical grounds, there was no improvement with the intravenous administration of a

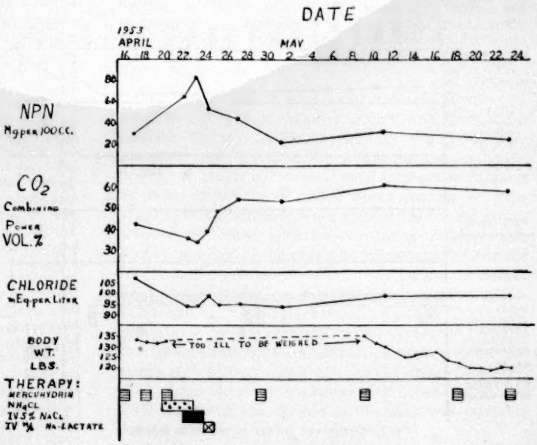

Fig. 1.—Course and therapy of patient in case 1.

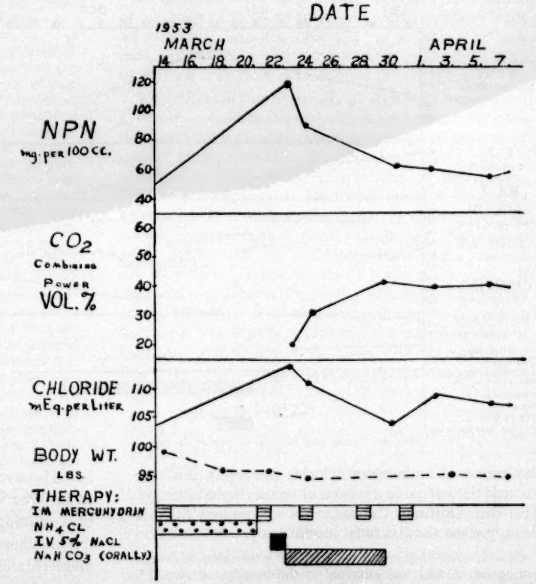

Fig. 2.—Course and therapy of patient in case 2.

hypertonic sodium chloride solution. The laboratory results then available should have suggested this result. When it was recognized that use of ammonium chloride might have precipitated the immediate illness and the patient was given therapy with an alkali, a favorable laboratory and clinical response was prompt. The seven-day course of ammonium chloride therapy in this case exceeds the advisable duration of uninterrupted therapy. This case illustrates the hazard of ammonium chloride therapy when there is renal insufficiency.

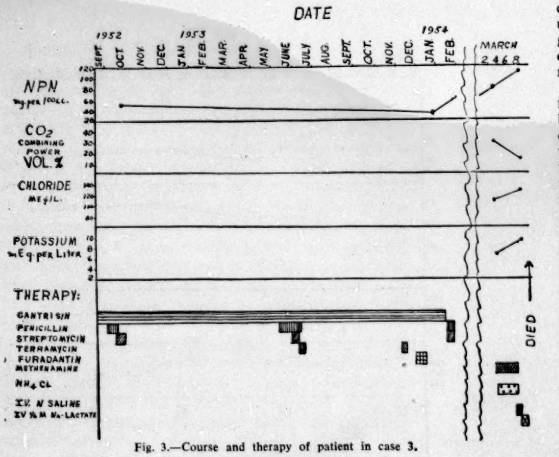

Fig. 3.—Course and therapy of patient in case 3.

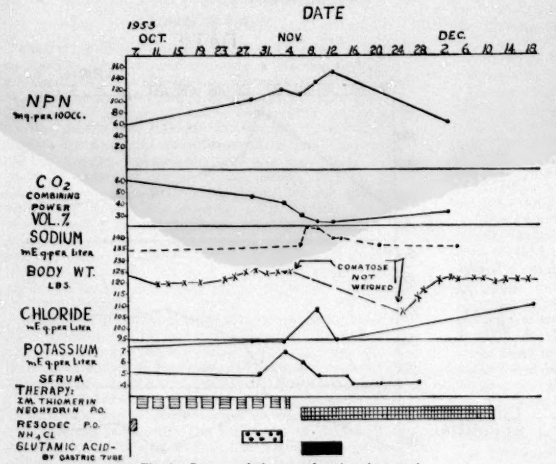

Fig. 4.—Course and therapy of patient in case 4.

CASE 3.—An 80-year-old male patient with taboparesis and neurogenic bladder was admitted to the hospital on Aug. 15, 1952, for treatment of chronic urinary tract infection. Catheter drainage had been used since April, 1951. Urine cultures consistently grew organisms of the Klebsiella-Aerobacter aerogenes group. Periodic acute episodes of fever, suprapubic pain, and bloody urine were controlled with use of antibiotics and chemotherapy. Because tests showed that only nitrofurantoin (Furadantin) inhibited growth of the infecting organism, this medicament was administered from Dec. 12 through Dec. 25, 1953. The urinary infection persisted, but, because of development of a progressive macrocytic anemia, use of the drug was discontinued. The hemoglobin level fell to 6.5 gm. per 100 cc. of blood on Jan. 8, 1954, but, thereafter, progressively returned to premedication level.

On March 2, 1954, it was decided to attempt further eradication of the urinary tract infection by administering methenamine mandelate (Mandelamine) 0.9 gm., three times a day, combined with ammonium chloride, 6 gm. daily. Examination of the patient at that time showed temperature to be 98 F (36.6 C), pulse rate 90, respiration rate 20, and blood pressure 130/70 mm. Hg. The patient was alert and cooperative. He had Argyll Robertson pupils, and tabes dorsalis was present. Observations of the heart and lungs were not remarkable. A retention catheter was in place. An indolent ulcer of trophic origin was over the left heel. On examination, urine was cloudy and alkaline and negative for sugar, with many bacteria. There were 150 white blood cells and 50 red blood cells per high-power field, 3+ albumin, and a specific gravity of 1.003. The electrocardiogram was considered a normal tracing. Results of other pertinent laboratory tests are summarized in figure 3.

Course.—After four days of combined methenamine mandelate and ammonium chloride therapy, the patient became dyspneic, with Kussmaul's respiration. The blood nonprotein nitrogen value was 115 mg. per 100 cc. and the carbon dioxide–combining power 13 vol. %. Use of these medicaments was discontinued, and an attempt was made to correct the acidosis with the intravenous administration of M/6 sodium lactate, at the rate of about 300 cc. per hour. However, the patient became progressively more comatose, developed marked pulmonary edema, and died on March 9, 1954, which was seven days after the ammonium chloride was first given. Autopsy revealed severe pulmonary edema, pericarditis (presumably uremic), pyonephrosis, severe chronic inflammation of the constricted urinary bladder, and adenocarcinoma of the prostate, which had invaded the bladder.

There are at least three underlying factors in the illness of this patient that may have influenced the rapid fatal outcome after administration of ammonium chloride: (1) hydrostatic renal impairment due to prostatic obstruction; (2) urinary disease related to chronic pyelonephritis and cystitis; and (3) a moderate degree of anemia. Ammonium chloride was administered to acidify the urine and enhance the bactericidal effect of methenamine mandelate. However, in spite of progressive metabolic acidosis, at no time was the urine acidified, possibly due to a urea-splitting urinary tract bacterial flora. In retrospect, the likelihood of benefit from administration of ammonium chloride in this patient seems less than the risk involved. In severe acidosis of this degree, use of a more

concentrated solution of sodium lactate would have been advantageous in hastening electrolyte correction without incurring undue risk of pulmonary edema from excessive fluid administration. The underlying disease processes in this elderly patient, particularly the locally invasive prostatic carcinoma, would almost certainly have caused his death within a limited time. However, he was in the process of apparent recovery from secondary anemia when ammonium chloride administration was begun. The rapid fatal course again illustrates the potential danger of the use of this medicament when there is renal insufficiency.

CASE 4.—A 60-year-old male was admitted to the hospital on July 13, 1953, in severe congestive heart failure. He was known to have had rheumatic heart disease for approximately 34 years and had shown evidence of cardiac insufficiency for at least one year. During this latter period he had exhibited classic signs of mitral stenosis, including chronic atrial fibrillation. A large pulsating liver, ascites, and massive leg and thigh edema had also been noted. Because of a history of prolonged excessive alcohol intake and laboratory evidence of chronic hepatitis, it was felt that the liver enlargement was probably due to a combination of Laennec's cirrhosis and passive congestion. In spite of regulation of digitalis dosage, rigid restriction of sodium intake supplemented by use of Resodec, a cation-exchange resin, and administration of mercurial diuretics, including mercaptomerin (Thiomerin) sodium, frequent paracentesis was required to relieve abdominal discomfort due to massive ascites. On Oct. 26, 1953, it was decided to attempt potentiation of the mercurial diuretic effect by administering ammonium chloride.

At that time, on physical examination of the patient, temperature was 97.4 F (36.3 C), pulse rate 88 (irregular), respiration rate 22, and blood pressure 120/70 mm. Hg. The patient was moderately dyspneic. His neck veins were distended and pulsating. The heart was enlarged and had an irregular rhythm. Loud, harsh apical systolic and diastolic murmurs were heard. A large, smooth, nontender pulsating liver was palpated 7 cm. below the right costal margin. The spleen was not palpated. There was no jaundice. There were massive ascites and pitting leg and thigh edema. He was mentally alert, rational, and well oriented.

An electrocardiogram revealed auricular fibrillation with frequent premature ventricular contractions and evidence of digitalism. The white blood cell count and differential were normal. Hemoglobin level was 10.2 gm. per 100 cc., and hematocrit was 33%. Urine values were within normal limits except for 1+ albumin. The specific gravity of urine was 1.016. The total serum protein level was 5.1 gm. per 100 cc., with albumin 3.5 gm. and globulin 1.6 gm. The total serum bilirubin level was 2.4 mg. per 100 cc. The cephalin flocculation test was 1+, thymol turbidity 2.8 units, prothrombin activity 82%, and sulfobromophthalein test 57% retention in 45 minutes. The serum electrolyte values were carbon dioxide–combining power 60 vol. %, chloride 93 mEq. per liter, and potassium 5.2 mEq. per liter, and nonprotein nitrogen level 59 mg. per 100 cc. (fig. 4).

Course.—The patient inadvertently was given 6 gm. of ammonium chloride daily for seven consecutive days instead of the intended four days a week. On the sixth day of drug administration, the patient was drowsy and listless. The error in ammonium chloride dosage was discovered the following day, and administration was discontinued. However, the patient became more lethargic and confused. On the night following the discontinuance of therapy, the patient climbed over the siderails of his bed and urinated on the floor. Mistaking the thermometer in his mouth for a cigarette, he attempted to light it. On examination at this time the previous physical abnormalities were unchanged. In addition the patient was disoriented as to time and place and responded to questions only after considerable effort. There was a flapping-type tremor of outstretched hands, suggestive of the precomatose stage of hepatic coma.

It became necessary to administer feedings through a gastric tube or intravenously for 18 days due to the patient's comatose state. Urinary output was adequately maintained. Therapy with chlormerodrin (Neohydrin) was begun at this time. Between gastric feedings, 2 gm. of glutamic acid was given in an aqueous alkaline solution every three hours through the stomach tube. Although there was mild fluctuation of the comatose state, no definite beneficial effect could be attributed to the administration of glutamic acid. On the fourth day of coma, the patient briefly responded appropriately to simple questions with "yes" and "no." By the 14th day his lucid intervals had become longer, although he continued to pull out the gastric tube if not restrained. On the 18th day, he was able to sit up and eat for the first time. At that time he was oriented in all spheres, and his mental status was considered to have returned approximately to that prior to the onset of coma. The patient was discharged from the hospital Dec. 14, 1953, still in marked congestive heart failure but mentally alert.

The serum chloride level was temporarily slightly elevated in this patient, as often occurs with ammonium chloride therapy. Although acidosis and moderately severe azotemia occurred, the carbon dioxide–combining power was nearly as low on clinical recovery from coma as in the stage of most severe stupor (see fig. 4). This suggests that acidosis was not responsible for the symptomatology. Since ammonia-containing products are poorly tolerated in patients with impairment of hepatic function, the comatose state in this patient was most likely related to the liver disease. Administration of glutamic acid had no apparent beneficial effects. There was, however, a definite relationship of the onset of coma to the administration of ammonium chloride and the patient's slow recovery after cessation of therapy with this drug. Since the cation-exchange resin Resodec contains 78% ammonia ion, its use in this case was probably inadvisable.

Comment

Ammonium chloride produces its undesirable effects in two ways: (1) by its acidifying property, which leads to metabolic acidosis, and (2) by releasing an ammonium radical, which may produce toxic effects with or without concomitant electrolyte disturbances.

Toxic Effects Due to Acidifying Action of Ammonium Chloride.—Ammonium chloride is administered in conjunction with mercurial diuretics in order to prevent or correct unresponsiveness to these drugs. This effect is presumably produced by replenishing or maintaining blood chloride levels.[1] Mercurial diuretics ordinarily cause a more excessive urinary loss of chloride than of sodium,[2] and mild alkalosis may result, with concomitant poor diuresis. But, the acidifying action of the chloride ion may lead to frank metabolic acidosis, especially if the renal regulatory mechanism is abnormal. The kidney status, therefore, is of prime importance in estimating how large a dose or how prolonged an administration of this drug may be tolerated. Even with normal kidney function, significant acidosis may be produced with a large dose. Sartorius, Roemmelt, and Pitts [3] brought about acidosis in normal subjects by administering 15 gm. of ammonium chloride daily for two days and 10 gm. for the next three days.

In 1925, Keith and others [4] reported a case in which the giving of 25 gm. of ammonium chloride over a period of five days to a nephritic patient resulted in severe acidosis and azotemia. Recently, Sleisenger and Freedberg [5] reported six cases of severe acidosis resulting from therapy with ammonium chloride in the generally given daily doses of 6 to 8 gm. All these patients

had evidence of renal disease. The contraindication of ammonium chloride therapy in the presence of impairment of kidney function is stressed in numerous current textbooks.

Laboratory studies [6] of patients with toxic conditions caused by ammonium chloride have shown an initial elevation of plasma chloride levels and a depression of plasma bicarbonate levels. The fixed alkali is lost in the urine, with lowering of the hydrogen-ion concentration of the blood. Clinically, the patient is lethargic, anorectic, and nauseated, with or without vomiting. Hyperventilation progressively develops and may become Kussmaul in type. After variable periods, there is dulling of the sensorium, and, if alkali therapy is not instituted, a deep coma may end in death. The loss of fixed alkali and water that occurs in acidosis leads to a decrease in urea clearance and a rise in the level of nonprotein nitrogen.[6a] Although uremia may contribute to mental dulling, the severe acidosis itself may be responsible for a deepening coma.

Proper therapy may be delayed due to an erroneous diagnosis of cerebral vascular accident, diabetic coma, terminal renal disease, or low-salt syndrome. Although the low-salt syndrome [7] may produce an elevated level of nonprotein nitrogen, both the plasma chloride and sodium levels are low in this condition, in contrast to the usually elevated chloride level in a toxic condition resulting from use of ammonium chloride. Furthermore, acidosis does not occur due to a low-salt syndrome.[8]

Ammonium chloride must be considered a potentially hazardous drug. Its use should be preceded by an appraisal of kidney function and guided by a series of electrolyte determinations. Renal insufficiency is a relative contraindication to its use, necessitating more vigilant observation. Both the dosage and the duration of therapy play a role in its toxicity. It is probably unwise, and usually unnecessary, to use the drug more often than for four consecutive days a week or in amounts greater than 8 gm. a day. Ammonium chloride is primarily used in the treatment of patients with congestive heart failure who are receiving mercurial diuretics and who have no evidence of renal disease. Use of this drug as an acidifying agent in urinary tract infections may be particularly hazardous because of the possibility of patients having renal impairment. The fact that the urine often is not acidified suggests that the therapeutic efficacy is negligible, although the risk involved is great, as shown by the fatal outcome of the third case in this report.

In the absence of intrinsic renal disease, the treatment of a toxic condition caused by use of ammonium chloride may require only the discontinuance of administration of ammonium chloride. More severe toxic reactions, especially when accompanied by renal disease, require use of large doses of sodium salts intravenously, by mouth, or by gastric tube, in the form of sodium lactate or sodium bicarbonate. Therapy with an alkali, with correction of acidosis, usually produces clearing of the sensorium within a relatively short period, although the correction of the azotemia may be less rapid.[2]

Toxic Effects Due to Ammonium Ion.—The chloride ion of ammonium chloride is excreted directly into the urine in combination with ammonia manufactured by the kidney or with the fixed alkali if there is renal impairment. The ammonium radical, however, is converted to urea chiefly by the liver prior to excretion, although a small portion is excreted directly as the ammonium ion.[8] In hepatic disease, there may be impairment of the handling of ammonium. Kirk [9] observed in 1936 that severe liver disease was accompanied by elevation of blood ammonia levels. The ammonia presumably originates in the intestine in these cases due to bacterial action, and, with liver dysfunction, the eradication from the blood of absorbed ammonia is abnormal.

The recent studies of Gabuzda, Phillips, and Davidson [10] strongly suggest that the administration of ammonium-containing drugs to patients with liver impairment can produce a form of hepatic coma. They noted that a significant number of patients with cirrhosis of the liver who were given ammonium-containing cation-exchange resins developed symptoms of impending hepatic coma. Administration of hydrogen-ion resins did not produce these symptoms. Further studies [11] revealed that symptoms of hepatic coma could be provoked in patients with cirrhosis of the liver by the administration of ammonium chloride, ammonium citrate, urea, or significantly elevated dietary protein. Other investigators have obtained similar results.[12]

It should be emphasized that the diagnosis of hepatic coma is a clinical one. There are no distinctive laboratory tests. Although electrolyte disturbances may occur, their correction apparently does not influence the depth of coma. Furthermore, hepatic coma occurs without any consistently detectable disturbances of electrolytes. Typically, restlessness and confusion develop, followed by drowsiness, deepening coma, and often death. A tremor characterized by flapping of the outstretched hands often appears in the precomatose stage and is suggestive but not diagnostic of the condition.[13] Typical electroencephalographic changes also occur but, again, are not pathognomonic.[14]

Although a definite causative relationship cannot be ascribed to the ammonium ion in spontaneous hepatic coma, it is evident that use of this substance can induce a similar state, demonstrated by electroencephalographic changes and a "flapping-type" tremor.[11] It is known that ammonia is toxic to the central nervous system and that glutamic acid has a unique protective function of binding this ion.[15] Consequently, glutamic acid recently has been administered for therapeutic purposes in hepatic coma. Walshe [16] has reported apparent benefit from this drug, but Webster and Davidson [17] were unable to influence hepatic coma significantly with glutamic acid. The fourth case reported here showed a negligible response by the patient to glutamic acid in what is presumed to be an example of ammonium chloride–induced hepatic coma. Thus far, nothing beyond supportive therapy is of proved benefit in this entity.[17]

The evidence at hand is sufficient to contraindicate the use of ammonium-containing products in the presence of hepatic dysfunction. Phillips, Schwartz, Gabuzda, and Davidson [11] reported that, in all of the cases of cirrhosis of the liver observed by them in which coma was induced by administering ammonium-containing substances, the coma was reversible. Nonetheless, in the fourth case report in this study a precarious state followed administra-

tion of ammonium chloride, suggesting that use of the drug can be hazardous in patients with impaired hepatic function.

Summary

In four cases studied a toxic condition was induced by use of ammonium chloride. The useful function of this drug in preventing a hypochloremic alkalosis and poor diuretic response to mercurials is not minimized. However, it is stressed that ammonium chloride may induce severe toxic conditions, particularly in the presence of renal or hepatic disease. With kidney function impairment, progressive hyperchloremic acidosis may occur. In the presence of liver disease, a state similar to spontaneous hepatic coma may be produced. This is presumably due to an excessive accumulation of the ammonium ion, which is toxic to the central nervous system.

It is felt that the renal and hepatic status should be determined prior to ammonium chloride therapy. During treatment, periodic electrolyte determinations are indicated. Misinterpretation of the adverse course that, at times, follows therapy with this drug is a primary deterrent to proper treatment. Initially, in the treatment, administration of ammonium chloride should be discontinued. Acidosis may then be combated with sodium salts, but no specific therapy is known that will influence the recovery from hepatic coma.

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A CONTROLLED STUDY OF CORTISONE THERAPY FOR HEADACHE AFTER PNEUMOENCEPHALOGRAPHY

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• Cortisone in dosage of 50 mg. every six hours for a total of 400 mg. was given orally to 50 patients after pneumoencephalography; 47 similar patients received a placebo. The two groups were then compared as to the incidence, severity, and duration of headache following this procedure.

The patients who received cortisone did better than the contratest group, and the difference was statistically significant in patients whose symptoms had an organic rather than psychogenic basis.

Patients who received 70 to 150 cc. of air (or oxygen) suffered as severely on the first day as did those who received 155 to 315 cc., but the relief afforded by cortisone was more striking in those who received the larger volume of gas.

The importance of the pneumoencephalogram as a diagnostic tool in the study of intracerebral lesions is generally accepted. Even though the procedure is not without hazard, the risk to the patient is sufficiently low, if wise selection is practiced, that it may be used without hesitation. The only deterring feature is the severity of the reaction experienced by the patient, manifested by a severe, throbbing, persistent headache, frequently associated with nausea and vomiting, aggravated by movement, and lasting one to six days after the procedure.

Bohn [1] found that only 8.4% of 1,000 patients were free of headache after pneumoencephalography. Simple lumbar puncture has been recorded by Shaw [2] as resulting in headache in 9% of patients; Krueger and associates [3] noted an incidence of headache after spinal anesthesia in 10.7% of patients. Huston and Lebherz [4] found the reported incidence of headache after spinal anesthesia in obstetrics to range from 5 to 20%. Sicard [5] was the first to postulate that headache after spinal puncture was due to an interference in cerebral hydrodynamics because of a persistent leakage of cerebrospinal fluid through the puncture hole. This theory is accepted by Krueger's group, Greene,[6] Thorsén,[7] and many others. The theory has been advanced that the symptoms are due to rapid expansion of the injected air

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The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

as it increases from room to body temperature, causing dilatation of the ventricles and resultant headache, but Bohn has observed that the same reaction occurs in patients in whom air did not reach the ventricles. Bickerstaff [8] has proved that a pronounced increase in the number of cells in the cerebrospinal fluid begins immediately after pneumoencephalography and that the period of greatest subjective discomfort corresponds to the period of greatest polymorphonuclear leukocytic reaction. He concluded that the symptoms are the result of an inflammatory meningeal reaction caused by the irritant properties of the substance injected. This theory is accepted by Schwab and von Storch [9] and by Fleck and Stein.[10]

Because of the lack of unanimity of opinion regarding the cause of these postencephalographic symptoms, it has been difficult to develop any satisfactory method of active treatment or prophylaxis. This is immediately apparent when one notes the variety of treatment proposed in the literature. The work of Bickerstaff and of others supplies a rational background for the study of the use of cortisone, an anti-inflammatory drug, in controlling the postoperative morbidity associated with pneumoencephalography.

TABLE 1.—*Clinical Diagnoses in Ninety-Seven Patients with Postpneumoencephalographic Headache*

Diagnosis	Total	Males	Females
Psychogenic headache	17	5	12
Convulsive disorder	26	17	9
Cerebral degeneration	33	19	14
Indeterminate cerebral lesion	7	2	5
Multiple sclerosis	3	0	3
Post-traumatic headache	2	2	0
Ménière's disease	1	0	1
Amnesia	1	0	1
Vascular lesion	2	1	1
Postectamptic seizures	1	0	1
Barbiturate intoxication	1	1	0
Porencephaly	1	0	1
Brain tumor	2	1	1
Total	97	48	49

Present Study

All pneumoencephalograms performed at the Mayo Clinic from Dec. 16, 1952, to Nov. 9, 1954, were screened immediately after they were done. All patients more than 17 years of age for whom no further procedure was contemplated or in whom there existed no contraindication to the administration of cortisone were included in the study. Each patient received a special medication containing either cortisone or a placebo, the contents being unknown to the examiners. An attempt was made to begin its administration as soon as recovery from the anesthetic agent permitted oral intake. No change was made in the usual postoperative regimen other than the administration of the unknown medication.

All pneumoencephalograms were performed with the patient under anesthesia produced by thiopental (Pentothal) sodium, with the exception of one patient who received local anesthesia. Air was used in 93 patients and oxygen in 4. The "complete" technique was used on all patients, which means that an attempt was made to remove all cerebrospinal fluid and replace it with an equivalent quantity of gas.

The dose of cortisone was 50 mg. every six hours for a total of 400 mg.; it was administered orally. This dose was considered to be great enough to eliminate the factor of insufficient medication, yet neither the total dose nor the duration of administration of the agent was thought sufficient to cause any serious adrenal dysfunction.

A total of 97 patients was included in this series; 50 of them received the afore-mentioned dose of cortisone and 47 received an inert placebo that was identical in appearance to the cortisone. No one active in the study had any knowledge of which patients were treated with cortisone until the study was completed and the results tabulated. Thus, since the examiners had no possible knowledge of the medication given, their evaluation of the severity of the headaches was not influenced.

Evaluation of the Headache.—In order to make the study as objective as possible, the following classification of the postpneumoencephalographic reaction was devised: grade 0 indicates no headache at any time; grade 1 indicates minimal headache on change of position, with the patient able to be up and about and to eat; he was frequently dismissed with this grade of headache; grade 2 indicates severe headache on sudden change of position but minimal to absent headache at rest, with the patient able to be up; grade 3 indicates severe headache, aggravated by change in position, with the patient confined to bed; and grade 4 indicates severe headache, with nausea and vomiting; the patient lies quietly in bed, afraid to move because of aggravation of headache. Evaluations were made each evening beginning with the day of operation, which is considered as the first postoperative day.

Composition of Series as to Sex and Age.—There were 48 male and 49 female patients included in the study. The ages ranged from 17 to 65 years in the males and 18 to 66 years in the females, with an average age of 42.7 in the former and 42.2 in the latter; 78% of the patients were between the ages of 30 and 59 years.

Composition of Series as to Final Clinical Diagnosis.—The final clinical diagnoses are summarized in table 1. It was finally determined in 17 patients that psychogenic factors were the basis for the symptoms, which were usually headaches. The remaining patients could be classified as having diseases that had some specific cause or organic basis; the majority of these had convulsive disorders or cerebral degeneration.

Results

Incidence by Grade of Headache.—The distribution of patients by grade of headache for the first postoperative day (day of operation) and the second postoperative day is presented in table 2. The only appreciable difference in the incidence of the five grades of headache on the first day between patients receiving cortisone and those receiving placebos was in the category graded 4, in which there were four times as many patients in the control group as in the treated group. However, when the grade 3 and the grade 4 categories were combined, the incidence was found to be equal.

On the second postoperative day, which should be a more reliable index since the patients had recovered from anesthesia and were better able to retain the medication orally, twice as many patients without headache were found in the group receiving cortisone as in the control group. Combining categories graded 0 and 1 gave an incidence of 68% for patients receiving cortisone and 57.4% for controls, an increment of 10.6 percentage points in favor of cortisone. A combination of categories 3 and 4 contained almost twice as many patients who received placebos as it did patients receiving cortisone. In a comparison of results on the first and on the second postoperative day, it was noted that the combined incidence of headaches graded 3 and 4 in patients receiving cortisone decreased from 38% on the first day to 8% on the second day, a decrease of 30 percentage points. Likewise, the decrease in control patients in the same categories was from 38.3 to 14.9%, a decrease of 23.4 percentage points. The difference in these two decreases is 6.6 percentage points in favor of cortisone. None of these percentages is statistically significant, but they indicate a trend that appears to favor consistently the group treated with cortisone.

TABLE 2.—*Incidence by Grade* in Treated and Control Groups with Postpneumoencephalographic Headache*

	First Postoperative Day				Second Postoperative Day			
	Treated		Control		Treated		Control	
Headache, Grade	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
0	1	2.0	2	4.2	8	16.0	4	8.5
1	10	20.0	7	14.9	26	52.0	23	48.9
2	20	40.0	20	42.6	12	24.0	13	27.7
3	17	34.0	10	21.3	3	6.0	4	8.5
4	2	4.0	8	17.0	1	2.0	3	6.4
Total	50	100.0	47	100.0	50	100.0	47	100.0

* See text for definition of grades.

Improvement.—Improvement of the individual patient was defined as being a change from the grade of headache on the first postoperative day to a lesser grade on the second day. There were found to be 35 patients (70.0%) who became significantly improved in the group receiving cortisone as compared to 26 patients (55.3%) who improved in the control group. Again, the difference of 14.7 percentage points is not statistically significant but indicates a definite trend in favor of the use of cortisone.

TABLE 3.—*Comparison of Results in Treated and Control Groups with Postpneumoencephalographic Headache by Diagnosis*

			Improved		Not Improved		No Headache	
Clinical Diagnosis	Group	Total Patients	No. of Patients	%	No. of Patients	%	No. of Patients	%
Psychogenic disease	Treated	10	5	50.0	5	50.0	0	...
	Control	7	5	71.5	2	28.6	0	...
Organic disease	Treated	40	30	75.0	9	22.5	1	2.5
	Control	40	21	52.5	17	42.5	2	5.0
Total.....		97	61	62.9	33	34.0	3	3.1

Clinical Diagnosis.—When the patients were divided into those having psychogenic conditions and those having organic disease (table 3), it was found that those in the psychogenic group responded best to the placebo. It may be assumed from this that, regardless of the treatment used, those patients whose symptoms are entirely on a psychogenic basis will respond erratically. However, with regard to improvement in the organic group, a difference of 22.5 percentage points was found between those who received cortisone and the control group; this figure is statistically significant.

Hospital Stay.—The hospital stay of each patient was recorded, the day of operation being counted as one, the day after operation as two, and so on; the day of dismissal from the hospital or from the neurosurgical service was considered as the last day. It will be noted from table 4 that the patients who received cortisone remained hospitalized on an average of a half a day less than did those receiving placebos. Those receiving cortisone and showing improvement remained in the hospital one day less than did those showing no improvement. These small differences again are not significant but indicate that the use of cortisone is of value.

TABLE 4.—*Comparison of Hospital Stay in Treated and Control Groups with Postpneumoencephalographic Headache*

	Total			Improved			Not Improved		
Group	No. of Patients	Total Hospital Days	Average Hospital Stay	No. of Patients	Total Hospital Days	Average Hospital Stay	No. of Patients	Total Hospital Days	Average Hospital Stay
Treated	49	186	3.8	35	124	3.5	14	62	4.4
Control	45	191	4.2	26	106	4.1	19	85	4.5
Total	94*	377	4.0	61	230	3.8	33	147	4.5

* Three patients in whom headache never developed are omitted.

TABLE 5.—*Results According to Amount of Gas Used in Treatment of Postpneumoencephalographic Headache*

			Improved		Not Improved		No Headache	
Amount of Gas Used, Cc.	Group	Total Patients	No. of Patients	%	No. of Patients	%	No. of Patients	%
70-150	Treated	24	16	66.7	7	29.2	1	4.1
	Control	27	17	63.0	9	33.3	1	3.7
155-315	Treated	26	19	73.1	7	26.9	0	...
	Control	20	9	45.0	10	50.0	1	5.0
Total		97	61		33		3	

Effect of Quantity of Gas Introduced.—The amount of gas introduced into the spinal canal ranged from 70 to 315 cc. Table 5 indicates that two-thirds of the patients to whom 150 cc. or less of gas was administered showed improvement, but no difference was evident between those receiving cortisone and the controls. However, those patients who received 155 cc. or more of gas appeared to show a pronounced response to cortisone, there being a difference of 28.1 percentage points in favor of the treated group.

Comment

An attempt was made in this study to set up a situation in which the usual criticisms of an evaluation of the effectiveness of a form of medication could be avoided. The natural and unavoidable tendency of observers to be influenced by knowledge of the treatment given each patient was avoided by distribution of the potent medication and the placebo in a random manner as unknowns.

As already indicated, none of those active in the study had any knowledge of which patients were treated with cortisone until the study was completed and the results tabulated.

It is exceedingly difficult to make a consistently accurate evaluation of a factor as subjective as a headache. In this study, the approach was designed to be as objective as possible by the use of certain relatively tangible factors, such as aggravation of headache by change of position, ability to be up and about, and the presence of nausea and vomiting. The patients' statements as to the severity of the headache were utilized as little as possible.

The most serious technical defect of the study was the use of oral rather than parenteral administration. It is well known that any potent medication is more effective when administered parenterally. This is especially true immediately after operation, when patients have difficulty taking preparations orally and retaining them. However, in order to maintain the controls of the study and to avoid subjecting patients to repeated hypodermic injection of a placebo, the oral route was used throughout. The number of patients who did not receive the benefit of the medication because of emesis or who were delayed in receiving the medication because of slow recovery from anesthesia is not known but may be assumed to be equal in those receiving cortisone and those receiving placebos. The results probably would have been better had the cortisone been administered parenterally.

TABLE 6.—*Grade* of Headache in Forty-Seven Controls According to Amount of Gas Used in Cases of Postpneumoencephalographic Headache*

	First Postoperative Day, Amount of Gas				Second Postoperative Day, Amount of Gas			
	70-150 Cc.		155-315 Cc.		70-150 Cc.		155-315 Cc.	
Headache, Grade	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
0	1	3.7	1	5.0	2	7.4	1	5.0
1	3	11.1	4	20.0	14	51.9	11	55.0
2	12	44.4	8	40.0	9	33.3	4	20.0
3	6	22.2	4	20.0	1	3.7	2	10.0
4	5	18.6	3	15.0	1	3.7	2	10.0
Total	27	100.0	20	100.0	27	100.0	20	100.0

* See text for definition of grades.

In the evaluation of the over-all results, the conclusion may be reached that those patients receiving cortisone had less severe headaches, improved more rapidly, and had a shorter stay in the hospital than did those patients receiving placebos. Even though the differences between the two groups are, in general, not overwhelmingly significant, there is a consistent indication that cortisone is of value in the treatment of headache following pneumoencephalography. There is statistically significant evidence of the value of cortisone in the treatment of this complication in patients who have other than psychogenic symptoms.

It is interesting to note that measurable headache occurred on the first postoperative day in 94 of these 97 patients, an incidence of 96.9%. In two of the three patients who did not have headache, a diagnosis of degenerative cerebral disease was made; one of these two patients did not complain of headache at any time, even though the gas was introduced with the patient under local anesthesia. The third patient had porencephaly.

A comparison of the headaches of the control patients with regard to the amount of gas used revealed no significant differences on the day of operation (table 6). However, on the second postoperative day, 92.6% of those who received 70 to 150 cc. of gas and 80% of those who received 155 to 315 cc. had headaches of grade 2 or less, indicating that the amount of gas is not a significant factor in the immediate reaction but is a factor in the rapidity of recovery.

The response of these patients to use of cortisone appears to confirm Bickerstaff's conclusion that postpneumoencephalographic symptoms are due to an inflammatory reaction. Other factors undoubtedly contribute also to the postoperative morbidity. Two of these, the psychogenic character of the patient's condition and the quantity of gas introduced, have been emphasized in this study.

It is not suggested that use of cortisone is the final answer to this serious problem of postpneumoencephalographic morbidity. Its use should be considered in conjunction with all other methods of treatment that have proved of value in making the valuable diagnostic tool of pneumoencephalography more acceptable to the physician and the patient.

Since the headaches following spinal anesthesia are probably of the same cause as are those following pneumoencephalography, cortisone should be of value in their treatment. Again, it should be used in conjunction with other methods that have proved of benefit.

Summary and Conclusions

A controlled study indicates that oral use of cortisone is of value in the treatment of headaches following pneumoencephalography. The amount of gas introduced intrathecally during this diagnostic procedure has little effect on the severity of the reaction but does affect the duration of severe symptoms. Patients whose complaints are on a functional or psychogenic basis show no benefit from use of cortisone. Parenteral administration probably would improve the response to cortisone.

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BILATERAL STENOSIS OF RENAL ARTERIES AND HYPERTENSION

TREATMENT BY ARTERIAL HOMOGRAFTS

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• *Severe hypertension occurred in three young patients (ages 14, 15, and 25 years), apparently as a sequel to bilateral stenosis of the renal arteries. In two the stenosis was orificial and due to fibrous intimal proliferation; in the other, the oldest patient, it was associated with severe calcific atherosclerosis of the renal artery and aorta.*

The fatal course of the condition in two of the patients clearly demonstrated the need for correction of the renal arterial circulatory impairment. This experience led to recognition of the condition in the third patient and to relief of the hypertension by what is believed to be the first successful arterial homografting of both renal arteries.

This condition may represent a hitherto unrecognized syndrome of hypertension in adolescence and may result from a developmental defect in the formation of the renal arteries.

Goldblatt [1] in 1934 showed that partial compression of renal arteries with a metal clamp produces hypertension. Since then the clinical implications of experimental renal hypertension have been carefully studied. It is now generally accepted that various lesions of the renal arteries and of the kidneys may cause hypertension in human beings. Several recent reports [2] have called attention to obstructive lesions of one or both main renal arteries in patients presenting the syndrome of malignant hypertension as a sequel to the arterial occlusion. The indications for early definitive treatment for patients with this type of hypertension have been presented.[3] The possibility that, in certain patients, a blood vessel graft could correct the obstruction and thereby relieve hypertension without loss of the kidney has been considered.[4]

The purpose of this study is to describe three patients who had bilateral stenosis of the renal arteries with resultant hypertension. All three were young, and the renal arteries of each were obstructed by fibrous intimal proliferation. The oldest of the three patients also had extensive aortic arteriosclerosis associated with an aneurysm of the abdominal aorta. The experience with the first two patients established the need of corrective arterial surgery. Recent development of vascular surgery and improvement of the techniques of aortography have supplied all the necessary means for such treatment. The third patient was relieved of hypertension by correction of the stenosis of both renal arteries with arterial homografts. This is believed to be the first case in which bilateral renal arterial occlusions have been surgically corrected. One of the cases, case 1, has been described previously.[5]

Report of Cases

CASE 1.—A 14-year-old boy was seen in June, 1951, because of attacks of abdominal pain and hypertension. There was no family history of hypertension. He gave a history of intermittent pain in both flanks and in the abdomen. His blood pressure was 238/160 in the left arm and 256/100 mm. Hg in the left leg, and he had severe hypertensive retinopathy (grade 4). All tests of renal function gave normal results, and the urinary sediment was normal. Neurogenic, endocrine, cardiovascular, and intrarenal causes of secondary hypertension were believed to be excluded. The absence of proteinuria and other evidences of renal arteriolar disease in the face of severe hypertension pointed to the possibility of bilateral renal arterial occlusion. Intravenous urography revealed prompt and satisfactory excretion from both kidneys, although the right kidney was somewhat reduced in size. A translumbar aortogram, originally interpreted in 1951 as showing normal renal arteries and renal vasculature, on recent review showed poor filling of both renal arteries and their branches.

At operation the right kidney was smaller than the left, and no pulse was felt in the right renal artery. A right nephrectomy was done, and it was noted that blood did not flow from the aortic stump of the renal artery; a probe was passed that met resistance at the orifice of the renal artery. The boy died four days later of cerebral hemorrhage.

Autopsy demonstrated severe stenosis of the orifices of both renal arteries, of the superior mesenteric artery, and of the celiac axis, caused by fibrous proliferation of the intima with islands of lipophage infiltration. The kidneys, which had been protected from the impact of elevated blood pressure by the arterial stenosis, showed normal microscopic structures. Because the diameter of the aorta was smaller at the level of the renal arteries than it was above or below, the condition was called coarctation of the abdominal aorta. However, a review of the translumbar aortogram showed no narrowing of this segment of the aorta.

CASE 2.—A 23-year-old woman was first seen in June, 1950, because of tuberculous keratitis. For three years she had had recurrent attacks of girdle-like pain below the umbilicus that radiated to both legs. One year before she was examined here, she was told that she had hypertension with a systolic pressure of 180 mm. Hg. There was no family history of hypertension.

On examination in 1950, her blood pressure was 170/118 mm. Hg. Peripheral arterial pulsations were palpable, and the heart was normal. Examination of the eyes showed heavy corneal infiltration consistent with tuberculous keratitis; the fundi were not well visualized; the blood vessels appeared normal and the disks blurred. An intravenous urogram revealed a normal upper urinary tract with both kidneys of normal size.

In June, 1952, she was admitted to the hospital for treatment of hypertension. She described episodes of nausea and excitability, and she had also noticed a large "knot" in her abdomen. The fundi showed only moderate (grade 2) arteriolar constriction and sclerosis. The blood pressure was 160/120 mm. Hg. The heart was essentially normal. A firm abdominal mass was palpable just above the umbilicus. An intravenous urogram showed a normal left kidney. The right kidney was reduced in size and excretory function as compared to the urographic findings two years before. Urinalysis showed a trace of albumin and many red and white blood cells. On roentgenography the heart was normal and the lung fields were clear.

A diagnosis was made of aneurysm of the abdominal aorta. At laparotomy (June, 1952), an aortogram showed irregular dilatation of the entire lumbar aorta and an aneurysm in the

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lower portion. The right renal artery was infundibular in shape and tapered off into a narrow vessel 1 cm. from the aorta. The first part of the left renal artery was also infundibular in shape. Further along there was a short segment of stenosis, but, beyond this point, circulation into the left kidney appeared intact.

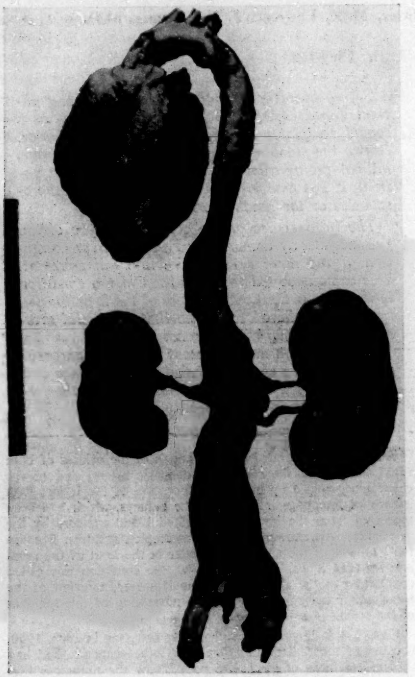

Fig. 1 (case 2).—Aneurysmal dilatation of lumbar aorta and atrophy of right kidney. Just beyond infundibular-shaped origins of both renal arteries are stenotic segments. Left ureter lies underneath aorta.

The aneurysm was wrapped with tantalum mesh, and the patient's immediate recovery was satisfactory. The average weekly blood pressure before surgery was 177/127 mm. Hg, and in the first few days after surgery it was 170/125 mm. Hg. One week postoperatively, retrograde brachial aortography was attempted, using 35 ml. of 70% iodopyracet solution, in order to further visualize the abdominal aorta and the renal arteries; but respiratory arrest occurred immediately after injection of the contrast medium. The patient was sustained in a respirator for five days before death.

The following pertinent findings were noted at autopsy: The heart weighed 275 gm. and showed no gross abnormalities. The aorta (fig. 1) showed focal arteriosclerosis of the thoracic portion, which became severe in the abdominal area, resulting in aneurysm of the lower portion. Both renal arteries were funnel shaped at their origin; the right, 0.5 cm. after its origin, showed circumferential calcification, resulting in almost total occlusion; and the left showed a contracted segment 1 cm. from the aorta. Histologically, there was nearly complete loss of elastic tissue in the region of the aneurysm in the aorta, with many areas of atherosclerosis and hyalinization. The origin of the right renal artery showed loss of elastic tissue and replacement by a calcific plaque. Distally, the lumen was concentrically narrowed by a relatively acellular, myxomatous-appearing tissue (fig. 2). The right kidney weighed 100 gm., appeared contracted, and possessed an irregularly scarred surface; microscopically, there was extensive glomerular fibrosis and some arteriolar sclerosis. The left kidney weighed 130 gm. and showed only one depressed scar in the inferior pole, which had irregular margins and a base measuring 1.2 cm. in greatest diameter. Microscopically, most of the left kidney showed only a moderate degree of arteriolar sclerosis; but the region of the scar contained many hyalinized glomeruli. On transection, the cortex of the right kidney measured 3.0 mm. in thickness and that of the left, 6.0 mm. in thickness. The brain was swollen and pultaceous and histologically necrotic.

This 25-year-old patient with a history of hypertension of at least three years' duration was found to have far-advanced aortic arteriosclerosis with aneurysm formation. Both renal arteries were abnormally shaped and were stenosed by subintimal calcified plaques and hyalinization resulting in scar formation and atrophy. The process was more severe on the right side. The renal arterial defects were apparently primary factors in the pathogenesis of the hypertension. The development at an early age of such advanced arteriosclerosis is most unusual.

Case 3.—A 15-year-old boy was well until March, 1955, when he developed intermittent generalized headaches. Five months later his blood pressure was observed to be elevated, with a systolic pressure of 180 mm. Hg. Two months later, he had a severe, brief attack of right midabdominal pain and was hospitalized for observation; findings on intravenous urography, chest roentgenogram, and laboratory studies were reported to be normal. Two weeks later he was readmitted to the hospital with severe pain in the left midabdomen and flank. The average blood pressure was 200/120 mm. Hg. The blood pressure in the left leg was 260/155 mm. Hg. He had another attack of severe abdominal pain associated with anxiety, during which time his blood pressure was 220/130 mm. Hg; phentolamine methanesulfonate given intravenously did not significantly alter the blood pressure. On Nov. 2 he was referred to the Cleveland Clinic by Dr. Francis J. Gaydosh of Wheeling, W. Va.

Fig. 2 (case 2).—Cross section of stenotic portion of right renal artery showing obstruction of lumen by fibrous proliferation of the intima. (× 15).

History was essentially noncontributory. Family history indicated that his father died at the age of 55 years with high blood pressure and renal complications; the nature of these is unknown. His mother and three siblings are living and well. On physical examination the blood pressure was 180/115 in the right arm and 210/120 mm. Hg in the right thigh. The fundi

revealed only mild (grade 1 to 2) constriction of the retinal arterioles. The pulse rate was 64 per minute. The heart sounds and peripheral pulses were normal. The average blood pressure during the first week of observation was 174/108 supine and 146/107 mm. Hg standing. An intravenous phentolamine methanesulfonate test was again negative. The electrocardiogram was normal.

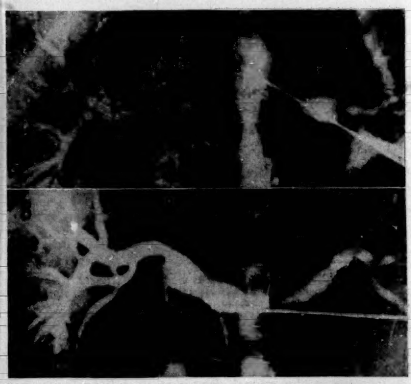

Fig. 3 (case 3).—*A*, preoperative aortogram showing stenosis of first portion of both renal arteries. Note distal dilatation of left renal artery. Intrarenal circulation is normal. *B*, postoperative aortogram showing restitution of renal circulation by arterial homografts.

Laboratory examination demonstrated a blood hemoglobin content of 13.6 gm. per 100 ml. and a white blood cell count 7,600 per cubic millimeter. The blood sugar content was 80 mg. per 100 ml. and the blood urea content 24 mg. per 100 ml. The urea clearance was 160 and 125% of normal after one and two hours respectively. A 12-hour Addis test revealed a urinary volume of 570 ml., specific gravity of 1.022, and proteinuria of 0.410 gm. per 24 hours. The sediment showed 1,600,000 white blood cells, 15,000 casts, and no red blood cells per 12 hours.

The chest roentgenogram was normal. An intravenous urogram showed prompt and satisfactory function of both kidneys, with no significant structural changes of either kidney. Translumbar aortography under local anesthesia revealed contracted origins of both renal arteries (fig. 3). The left renal artery was slightly dilated just distal to the narrowed segment. The arterial circulation throughout both kidneys otherwise was normal.

*Preoperative and Postoperative Excretory Functions of Both Kidneys of Patient in Case 3 Compared by Determinations of Urine Osmolarity and Electrolyte Concentrations**

	Sodium Level, mEq./ Liter	Potassium Level, mEq./ Liter	Osmolarity, mOsm.†/ Liter
Preoperative			
Left kidney	46.5	8.3	160
Right kidney	56.1	9.9	168
After 1st operation ‡			
Left kidney	18.6	9.3	90
Right kidney	11.0	9.7	82
After 2nd operation			
Left kidney	41	15.3	366
Right kidney	41	22	332

* Urine was collected separately from each kidney by ureteral catheterization.
† mOsm. = milliosmols.
‡ Intravenous infusion caused diuresis at time of collection.

Urine was collected separately from both kidneys and revealed satisfactory concentrating ability of each (see table).

First Operation.—At the first operation (Nov. 10, 1955), the left kidney was approached by a subcostal incision. The left renal artery, just distally to the abdominal aorta, was found to be narrowed to less than half the diameter of the remainder of the artery. A pronounced thrill was palpable. The kidney was soft and easily compressible but had a normal appearance. A special angled arterial clamp, designed by one of us (A. W. H.) to permit incision of the aortic wall without obstruction of blood flow, was applied to the aorta just below the narrowed renal artery. A lyophilized femoral artery homograft was sutured end-to-side to the incision in the aorta. The narrowed segment of renal artery was then ligated and excised. The homograft was sutured end-to-end to the normal portion of the renal artery close to the renal hilus. The kidney was deprived of arterial circulation for only five minutes. When blood began to flow through the homograft, the kidney immediately returned to normal color and became much firmer than it had been previously. Recovery from the operation was uneventful. Five days postoperatively an intravenous urogram showed both kidneys to be functioning normally. The average blood pressure during the first postoperative week was 164/100 supine; during the second week it was 167/103 mm. Hg supine.

Second Operation.—At the second operation, two weeks after the first operation, a midline approach was utilized to provide adequate access to the aorta and the right renal artery. The vena cava was retracted laterally to expose the narrowed portion of the renal artery that lay immediately beneath it. A distinct thrill was also palpable on this side. An arterial homograft was placed between the aorta and the distal normal renal artery in a manner similar to that utilized on the left side. Arterial circulation was restored within 14 minutes. The narrowed segment of renal artery was excised after ligation close to the aorta.

Two weeks after the second operation, samples of urine were collected from each kidney and analyzed (see table). Translumbar aortography revealed both renal artery homografts functioning normally with no evidence of interference with renal circulation. The average blood pressure during the first week after the second operation was 162/94 supine, and during the second week it was 140/84 mm. Hg. Six weeks after the second operation, he was well; the average blood pressure over a period of five days was 130/76 mm. Hg. The findings on intravenous urography were identical to those on the preoperative study. The aortogram showed both renal arteries functioning normally; the grafted segments appeared to be twice the size of the remainder of the arteries (fig. 3*B*). The blood urea content was

Fig. 4 (case 3).—Pathological changes in right renal artery. Selected cross sections comparing stenotic zone with more distal relatively uninvolved segment (Masson trichrome stain; × 15).

27 mg. per 100 ml. Three months after the second operation, he has remained in good health, except for occasional attacks of abdominal pain; the blood pressure is normal.

Renal Function Test.—Plasma clearances of *p*-aminohippurate (PAH) and mannitol were used as measures, respectively, of renal plasma flow and glomerular filtration rate. Preoperatively, the renal blood flow was 1,000 ml. per minute per 1.73 square meters of body surface, plasma flow 620, and glomerular filtration rate 111, with filtration fraction 0.18 and mean arterial pressure of 121 mm. Hg; these values are normal, except for the hypertension, and indicated increased resistance to renal blood flow. The second observation was done two days after placing the first renal artery homograft; the values for renal blood and plasma flow were, respectively, 637 and 414 ml. per minute and the glomerular filtration rate, 83 ml. per minute, with a filtration fraction of 0.2 and a mean arterial pressure of 150 mm. Hg. He was observed again two weeks after the second operation; the presence of a sulfonamide interfered with determinations of *p*-aminohippurate, but glomerular filtration rate was measured as 150 ml. per minute per 1.73 sq. m., which is in the high normal range.

Pathology.—The removed segment of left renal artery measured 0.7 cm. in length, 0.3 cm. in diameter; on cross section, approximately 75% of its lumen was symmetrically replaced by firm gray-white tissue locally stenosing the artery. The right renal artery segment measured 0.8 cm. in length, 0.4 cm. in diameter at one end and 0.3 cm. at the other. The narrowed end resembled the left renal artery. The artery segments were similar microscopically. The narrowed portion of left renal artery had a wall four times thicker than that of the relatively uninvolved portion (fig. 4). The intima was thickened by amorphous and finely fibrillary material that stained positively for collagen by the Mallory-Heidenhain, Masson trichrome, and Van Gieson connective tissue stains; embedded in it were fibroblasts and numerous longitudinally arranged cells resembling smooth muscle cells. The intima and internal elastic lamina were arranged in deep folds. The latter was focally reduplicated; as a result, the fibrous tissue occurred both between elastic tissue layers and deep to the elastic lamina. There was no lipid demonstrable. The smooth muscle coat of the artery in the stenotic area appeared to be intact; the external elastic lamina was prominent. Distally the artery was histologically normal.

Fig. 5 (case 3).—Photomicrograph of stenotic segment, demonstrating mural thickening by fibrous tissue and smooth muscle hypertrophy. Note absence of internal elastic membrane. (Verhoeff's elastic–Van Gieson stain; × 90).

Multiple sections of the stenosed portion of the right renal artery demonstrated a similar increase in mural thickness with deposition of collagenous material containing smooth muscle, which appeared to extend deeper into the muscular coat of the artery and separated small muscle bundles (fig. 5). The internal elastic lamina was completely absent; only a few scattered segments of the external elastic lamina were present, and these were fragmented and appeared embedded in collagen. A large amount of elastic tissue was present in the adventitia. A lipid stain (Sudan 4) demonstrated focal small areas of fat deposition immediately beneath the endothelium of the vessel and rare small aggregates scattered throughout the collagen but without any

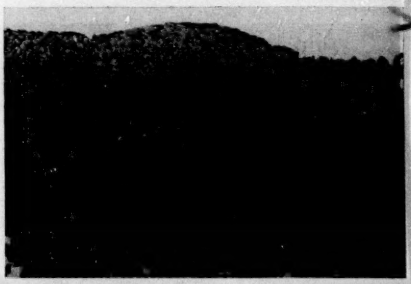

Fig. 6 (case 3).—Photomicrograph of more distal segment. Arterial wall at the exreme right appears normal. Intima is thickened by connective tissue. Note fraying and loss of internal elastic membrane (Verhoeff's elastic–Van Gieson stain; × 90).

evidence of phagocytosis. Sections of the vessel adjacent to the pronounced change showed a marginal area in which there was an increase in the intimal deposition of collagen with fragmentation and reduplication of the internal elastic lamina (fig. 6). Biopsy of the left kidney demonstrated no histological abnormalities.

Comment

Clinical and pathological findings in patients with hypertension resulting from obstructive lesions of the renal arteries have been reviewed in two recent reports.[4] The mechanism of hypertension in these cases is apparently identical with that of experimental hypertension caused by partial compression of the renal artery (Goldblatt). The lesions responsible include embolism, thrombosis, arteriosclerotic plaques, aneurysms, and syphilitic arteritis. The three cases described above have characteristics in common that permit them to be grouped together as a distinct form of renal hypertension resulting from arteriosclerotic disease of the renal artery that may be of developmental origin. These characteristics are the early age of onset of hypertension, the presence of bilateral lesions of the renal arteries, and the absence of any other ascertainable cause of the hypertension. The arterial lesions in the two boys (cases 1 and 3) were nearly identical, consisting of reduction of the external diameter of the juxta-aortic portions of renal arteries, with fibrous intimal hyperplasia at the orifices that extended 1 to 1.5 cm. along the courses of the vessels in one of the patients. Neither of these patients had microscopic renal lesions, which suggests that the renal arterioles had been protected from the impact of systemic hypertension by the stenosis of the renal artery.

The case of the 25-year-old woman (case 2) represents a much more advanced stage of arteriosclerosis, with involvement of the aorta as well as of the renal arteries. Plaques were present along the courses of both renal arteries, nearly obstructing the right renal artery, with resultant renal atrophy and, associated with this, lesions of arteriolar nephrosclerosis. The presence of the latter

lesions, together with the more advanced nature of the renal artery lesions, raises some question as to whether the mechanism of the hypertension and the pathology were basically the same as that of the two boys. However, the striking similarity of the pronounced change in the right renal artery suggests that it may have been the primary lesion and that the premature senescence of the abdominal aorta was secondary to the hypertension. On the basis of aortography and the study of the anatomic specimen, it is presumed that a similar obstructive lesion was present in the left renal artery.

When the cause of the fatal hypertension in the patient of case 1 was recognized, it was suggested that future instances of this condition should be amenable to surgical correction.[5] The excellent renal function in the patient of case 3 and the size of the renal arteries distal to the occlusion indicated that reparative surgery was feasible; death of the first patient showed it to be imperative. Repair consisted in surgical replacement of the obstructed segments of the renal arteries with lyophilized femoral artery homografts from the artery bank, done in stages at intervals of two weeks. Recovery of renal function after the brief intervals of ischemia was rapid; function, as estimated from the urogram and from measurement of glomerular filtration, was normal six weeks postoperatively. The postoperative aortogram showed both renal arteries to be fully patent and the blood flow good. As far as we are aware, this is the first patient in whom this two-stage operation has been performed as a means of relief of hypertension.

The origin of the renal artery stenosis in these three patients must remain speculative. The lesions in the three patients consisted of fibrous intimal hyperplasia and may represent merely a youthful form of arteriosclerosis [6]; that this is the nature of the lesion is suggested by the evidence of damage to the internal elastic lamellae of the renal arteries and also by the atheromatous-like character of the edges of the lesions, with lipid present in one of them. On this basis the lesions can be classed together as arteriosclerotic. The symmetrical character of the fibrous lesions and their occurrence in youth suggest that there may have been underlying developmental defects of the structure of the renal arteries that predisposed to premature arteriosclerosis. The calcified aortic and renal arterial plaques of the third case are indisputably arteriosclerotic and may represent an advanced stage of the process found in the other two and the end-results of persistent hypertension.[7] Instances of unilateral stenosis of one main renal artery, or of a branch thereof with similar intimal lesions, have been recorded [2c] but are tentatively considered distinct from the process described above.

Summary

Three patients had secondary renal hypertension caused by stenosis of both renal arteries. These cases had several common characteristics, notably the symmetrical nature of the renal artery lesions, the early age of onset of hypertension, and the lack of any other ascertainable cause of hypertension. The stenosis of the renal arteries resulted from fibrous proliferation of the intima and was associated with reduction in the external diameter of the involved segments of renal artery. The third patient, in addition, had an advanced state of calcified arteriosclerosis of both renal arteries and of the aorta with aortic aneurysm. The basic defects in these patients may be developmental flaws in the renal arteries. The first successful arterial homografting of both renal arteries for relief of hypertension was performed in one of these patients.

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Adrenalectomy for Cancer.—Bilateral adrenalectomy or this operation combined with oophorectomy have been carried out in 175 patients with advanced cancer of the breast. . . . The initial operative mortality of 5% has now been reduced to 1.4%. There has been no death in the last 65 cases. No operative morbidity has been observed in adrenalectomized patients. Medical management in these patients is not difficult. The hormonal substitution regimen employed . . . provides safe and adequate replacement in these patients. No postoperative death has been attributable to adrenal insufficiency. Adrenalectomy has induced significant and prolonged regression of extensive mammary cancers of women who had not responded to earlier treatment with testosterone, estrogen, oophorectomy, and irradiation of the ovaries. Six patients with widely disseminated mammary cancer have had profound regression of the cancer, which has persisted more than 30 months; one woman who had a rapidly advancing mammary carcinomatosis is in good health 49 months after adrenalectomy. The surgical methods are useful therapeutic agents in appropriate cases of cancer of the breast in the human male and female.

The mechanism of regression after adrenalectomy in cancer of the female breast seems to be the withdrawal of critical amounts of hormones similar to those found in the ovary. After adrenalectomy in women who have undergone oophorectomy the excretion of estrogen in the urine is abolished. Cortisone in the dosage of 100 mg. daily is capable of suppressing hypercalcuria and hypercalcemia in patients with extensive osseous metastases. We have observed remarkable symptomatic improvement, and high levels of serum calcium and urinary calcium excretion often return to normal after cortisone therapy. There is, however, no evidence of actual cessation of bone destruction in these cases. The use of sex steroids and cortisone in patients who fail to respond to adrenalectomy or to those who have relapse after a remission has not proved to be beneficial to these patients. Simultaneous bilateral adrenalectomy in a one-stage operation is a practical therapeutic device for selected cases of advanced mammary cancer. . . . It will provide profound and prolonged relief in a small percentage of patients.—T. L. Dao, M.D., and Charles Huggins, M.D., Bilateral Adrenalectomy in the Treatment of Cancer of the Breast, *A. M. A. Archives of Surgery*, November, 1955.

RAUWOLFIA-EPHEDRINE AS A HYPOTENSIVE-TRANQUILIZER

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• *Among 68 patients treated with Rauwolfia preparations, 20 developed some untoward side-effect. In three patients the prolonged administration of these preparations to relieve symptoms of hypertension resulted in the appearance of nasal congestion, excessive drowsiness, overeating, alarming nightmares, irrational behavior, and an incapacitating degree of agitated depression.*

In all cases it was found possible to continue the use of Rauwolfia preparations by adding ephedrine. The recommended dosage is 8 mg. of ephedrine with 100 to 200 mg. of the whole powdered Rauwolfia root or with 0.1 to 0.25 mg. of reserpine, the combined dose being given three times daily. The ephedrine in this dosage did not interfere with the hypotensive action of the Rauwolfia and did relieve the above-mentioned side-effects.

Rauwolfia serpentina is a medicinal herb of the dogbane group utilized for centuries in India for indications recently "discovered" by the modern world.[1] Originally, treatment with Rauwolfia was "rejected" by modern workers because it did not live up to Indian claims in the treatment of insanity. However, it was "accepted" as a hypotensive agent, largely because this effect could be objectively demonstrated without the requirement of fine clinical differentiation.[2] This work was begun as far back as 1931.[3] Rauwolfia has been used with boosters of other hypotensives, such as hydralazine (Apresoline),[4] veratrum,[5] hexamethonium,[6] neostigmine (Prostigmine),[7] or mannitol hexanitrate.[8]

All that has been said about Rauwolfia is applicable to extracts of Rauwolfia and to the crystalline alkaloid of Rauwolfia, reserpine, which was first isolated in 1936[9] and was further refined in 1953.[10] The single dose of the alkaloid is from 0.1 to 1.0 mg., the average being 0.25 mg., as compared with a dose of from 50-200 mg. of whole powdered root of Rauwolfia. The first American observers rejected Rauwolfia for use in "insanity." They "discovered," however, that its use in treatment of hypertension was attended by favorable results. Later, however, American observers found that Rauwolfia was useful in treating "anxiety, tension, nervousness, stress, and other nervous disturbances both in persons with normal blood pressure and in those with hypertension." [11] Thus the initial "rejection" by the first American observers for "insanity" and its later "discovery" for nervousness, anxiety, tension, and stress, becomes largely a matter of semantics. Perhaps in translation from the *Indian Medical World*, the word insanity was not properly translated in reference to its meaning, since the meaning of "insanity" in our Anglo-Christian civilization is a matter of legal definition having nothing to do with the syndromes of psychosomatic medicine. Consequently, the confusion originating in our words has now been cleared up, since the observations of the Indian doctors dating back many centuries have now received the stamp of scientific approval, having been brought into agreement with the observations of modern science. The use of Rauwolfia and of reserpine in treatment of conditions of anxiety, tension, nervousness, stress, and many other nervous disturbances is beginning to outweigh its usefulness for hypertension and is receiving greater and greater attention. The sedative and hypnotic action of Rauwolfia and of reserpine is now one of the most important advances in treatment of the mentally ill.[12]

Owing to the widespread use of Rauwolfia and reserpine for treatment of hypertension, of neurotic anxiety states, and of psychosis, any toxic manifestations or distressing symptoms induced as side-effects acquire great importance. In addition, it should be realized that the conditions for which Rauwolfia is used are essentially chronic in nature. Therefore toxic side-effects tend to limit its usefulness most seriously.

The materials used in this study were supplied by the S. E. Massengill Company, Bristol, Tenn., under the name Renir.

Side-Effects

The dangerous and distressing side-effects of Rauwolfia and reserpine may be divided into the following classifications: (1) smooth-muscle stimulation, (2) vasodilator effects, and (3) central nervous system depression. The action of Rauwolfia and reserpine on smooth muscle results in an increased number of bowel movements, characterized by diarrhea, and increased hunger. The vasodilator action results in troublesome nasal stuffiness in many cases. The central-nervous-system-depressant action results in excessive drowsiness, which is apparently quite common [13] and is responsible for mental depression found in patients treated for chronic hypertension. Freis[14] has collected and reported a series of patients having depression and lassitude after treatment. These patients usually became free of depression shortly after withdrawal of the drug. In addition to the signs and symptoms already discussed, nightmares and dreams of particularly violent character form a part of the syndrome of side-effects induced by Rauwolfia and reserpine. Particularly horrible dreams and frightening nightmares affect the psyche throughout the following day in such manner that the patient becomes depressed and disoriented, leading to many unfavorable psychological responses, which induce a condition of agitated depression.[14a]

All of these distressing and dangerous side-effects may be overcome by the use of small doses of ephedrine in combination with Rauwolfia or reserpine. The pharmacodynamic actions of ephedrine [15] may be described as (1) smooth-muscle relaxation, (2) vasoconstrictor action, and (3) central nervous system stimulation. Ephedrine as a smooth-muscle relaxant decreases movements of the uterus and intestine and relaxes the

bronchi. The vasoconstrictor action relieves nasal edema and stuffiness and, in experimental animals, under certain conditions of administration, raises blood pressure. The central-nervous-system-stimulating effect causes insomnia and mood elevation. There are three points of extreme interest not known about the effects of ephedrine that are not stated in the pharmacology books. In our experience ephedrine has had an anoretic effect in overcoming hunger in large groups of normal people who have a tendency to gain weight and in a group of persons in whom the appetite has been increased by treatment with Rauwolfia or reserpine, with weight gain. This anorectic action is similar to that found with the amphetamines but is more powerful. The exact mechanism of the origin of this hunger, though usually ascribed to the action of Rauwolfia in increasing propulsive movements of the gastrointestinal system, has not been clearly defined, but the hunger is completely overcome by the action of ephedrine. The origin of agitated depression and horrible dreams resulting in nightmares has not been clearly defined in the pharmacology of Rauwolfia and reserpine. No pharmacological study or report has been found of ephedrine overcoming this type of difficulty in normal people. Therefore relief was not expected as a result of treatment with ephedrine. However, just as the unexpected result of reversing hunger occurred, the nightmares and agitated depression were completely relieved by treatment with ephedrine when given simultaneously with Rauwolfia. One of the most interesting effects has been that ephedrine, in the small doses indicated (usually ⅛ grain [8 mg.]) with each dose of 100 mg. of whole root of Rauwolfia or 0.25 mg. of reserpine, did not interfere with the hypotensive action.

Report of Cases

CONFUSED DEPRESSION AND NIGHTMARES.—A 63-year-old man had shown the first signs of malignant hypertension five years previously. Two years previously his blood pressure had been 260/140 mm. Hg. At that time treatment with mannitol hexanitrate was instituted. Examination after treatment for a period of six months showed that the blood pressure was 200/120 mm. Hg. The fundi showed grade 3 changes, the heart was enlarged, and there was some pulmonary congestion. Various courses of treatment, including therapy with hexamethonium and pentolinium (Ansolysen) tartrate, were used. These resulted in various slight depressions of blood pressure. Six months previous he was given 0.25 mg. of reserpine three times daily. During the following months the average blood pressure was 150/90 mm. Hg, and the patient felt better. After treatment for three months he developed a depressed state. He was unable to leave the house to go to his office and stayed in bed for many days at a time. Physical examination showed some improvement, and the blood pressure remained constant at the low level of 150/90 mm. Hg. He began to complain of terrific hallucinated dreams, which were of such depressing and grave nature that they disturbed his psyche throughout the waking hours. These dreams were described as so horrible that he did not wish to tell anyone about them. During the day there was a state of confused depression. Attempts by a psychiatrist to establish rapport were not successful. All during this time he continued to eat well and to show no signs of physical depression except occasional stuffiness of the nose.

At this time it was decided to add ⅛ grain of ephedrine to each dose of 0.25 mg. of reserpine. As soon as this regimen was instituted, all signs of nasal stuffiness disappeared. Within three days the nightmares and disturbing dreams no longer occurred, and in addition he was able to establish contact with his environment in a manner reminiscent of that before medication with reserpine but in a more orderly and tranquil manner. He returned to work on a reduced schedule and has been successful for a period of eight weeks in establishing a work routine that is not burdensome. It is of interest to note that his blood pressure was unchanged, ranging from 150 to 160 mm. Hg systolic and from 88 to 95 mm. Hg diastolic. The dose of reserpine with ephedrine was taken early in the morning, at 11 a. m., and at 4 p. m. There was no interference with sleep.

This case illustrated increased tolerance to reserpine by addition of ephedrine when the side-effects of reserpine medication would ordinarily have made it impossible to continue with this form of hypotensive medication.

CONFUSED DEPRESSION, NIGHTMARES, HUNGER, INCREASED PERISTALSIS, AND WEIGHT GAIN.—A 65-year-old man had shown during the past 10 years an exacerbation of a psychoneurotic state that had been incipient all his life. His first episode occurred at about the age of 21 years. This consisted of a confining depression that lasted for approximately one year. During his life he had been subject to "nervous breakdowns." The diagnosis was that of a mild psychosis of a psychosexual nature. During the past 10 years he had complained of impotentia erigendi and at times had been subject to fits of depression. During the last episode, lasting six months in all, he became subject to fits of depression. He had been treated for the previous four months with 100-mg. doses of whole-root Rauwolfia three times daily. This induced a change of attitude in that he did not seem to care as much or worry as much about his physical complaint as he had previously. However, during the time of treatment and particularly during the last two months, he showed a tendency to gain weight. His usual weight was 145 lb. (65.8 kg.), and it gradually rose to 160 lb. (72.6 kg.). A thorough investigation elicited the complaint that he had approximately three bowel movements per day, as compared with a previous record of only one. His hunger was such that he ate about twice the usual amount of food. He had previously not eaten a sufficient amount to cause a gain of weight with his advancing age. Although depression had previously been present, it now was agitated and moderately severe. Agitation was evident in view of irrational modes of action. An illustrative episode was that, on an occasion of a call at a friend's house, he ran up and down the street shouting the names rather than waiting at the doorway. On previous occasions of depression, he had been quiet and withdrawn. Questioning revealed that nightmares were present but had had never occurred previous to the treatment with Rauwolfia.

This patient was considered to have an intolerance to Rauwolfia. One-eighth grain of ephedrine sulfate was administered by mouth on the occasion of each dose of Rauwolfia. The patient took, in combination, 100 mg. of whole-root Rauwolfia powder and ⅛ grain of ephedrine sulfate early in the morning, at 11 a. m., and at 4 p. m. There was no change in blood pressure, the blood pressure being 144/86 mm. Hg on the average before and after the change to the ephedrine component. Within a few days after beginning the treatment with ephedrine in combination with Rauwolfia whole-root powder, all the symptoms representing undesirable side-effects of treatment with Rauwolfia subsided. The number of bowel movements returned to one daily, hunger was decreased to approximately the normal state, nightmares disappeared, and the agitation accompanying the depression was considerably relieved. During the month immediately after the beginning of the addition of ephedrine to the regimen, the depression gradually subsided. During the following month treatment with Rauwolfia was withdrawn, and the patient reported that his feeling of detachment was lost and he felt that he would like to restart the treatment, in order to be less sensitive to his surroundings. Treatment with Rauwolfia and ephedrine was reinstituted, with good therapeutic response and no untoward side-effects.

This case illustrates the type of patient with smooth-muscle stimulation induced by Rauwolfia who has confused depression and nightmares. The smooth-muscle

stimulation of the intestine and stomach increases the number of bowel movements and at the same time increases hunger. This causes weight gain but is counteracted by the surprising amount of anoretic effect shown by ephedrine. At the same time the unexpected effect of relief from nightmare was noted.

NASAL CONGESTION AND EXCESSIVE DROWSINESS.—A woman 50 years of age was known to have had hypertension for the previous five years. The blood pressure was 242/110 mm. Hg. Within two months after administration of 100 mg. of whole-root Rauwolfia powder three times daily, the blood pressure was 165/98 mm. Hg, and many of the symptoms of the hypertensive syndrome, such as vertigo, shortness of breath, and flushing, were relieved. During this time nasal stuffiness, at first thought to be from a cold, became prominent, and there was excessive drowsiness during the day. A program of therapy, consisting of 100 mg. of whole-root Rauwolfia powder in combination with ⅛ grain of ephedrine three times daily, was instituted. Within one week the nasal stuffiness and excessive drowsiness were completely relieved.

This illustrates another case in which tolerance to Rauwolfia can be increased by the use of ephedrine in combination with Rauwolfia.

Comment

The foregoing cases have been selected because, taken together, they illustrate all of the side-effects of Rauwolfia or reserpine: (1) increased number of bowel movements, (2) nasal stuffiness, (3) hunger and weight gain, (4) excessive somnolence, (5) agitated depression, and (6) nightmares. The use of ephedrine has reversed all of these symptoms without causing the untoward side-effects attributed to ephedrine by classic pharmacological reports, which are (1) increased blood pressure and (2) insomnia.

It is obvious that these two drugs act together to give a true synergistic response in that the untoward effects of each are counteracted and the desirable therapeutic effects of each are enhanced. It has not been previously shown that use of ephedrine causes the following psychosomatic effects: (1) anoretic action with reversal of tendency to gain weight under influence of Rauwolfia, (2) relief from nightmares, and (3) relief of agitated depression.

A further example of the synergism involved is the not previously known fact that Rauwolfia completely prevents the action, if any, of ephedrine in raising blood pressure. Not only is the blood pressure not raised, but the blood-pressure-lowering effect, which is a property of Rauwolfia, is in no way impaired by its combination with ephedrine.

Out of a group of 68 patients treated with Rauwolfia or reserpine, 20 patients developed some untoward side-effect. In each case treatment with ⅛ grain of ephedrine sulfate in combination with 100 mg. of whole-root Rauwolfia caused complete relief with continued favorable therapeutic response. Physicians and psychiatrists should be encouraged to elicit reports of symptoms from the patient so as to prevent further development of these side-effects with consequent deleterious influence on the psyche. It is not sufficient to wait until the patient complains of diarrhea before the number of bowel movements is noted, nor is it sufficient to wait for periods of excessive hunger before weight gain is observed. Careful clinical evaluation of treatment with Rauwolfia or reserpine is still most necessary. This type of medication presages great future improvement in the treatment of psychic disturbances as well as hypertension. Use of such medicaments in chronic conditions should be carefully observed by the physician.

It is of philosophical interest to point out that ephedrine and Rauwolfia are two of the most ancient herbal remedies, ephedrine being a medicament known to the ancient Chinese with essentially the same indications as today and Rauwolfia being an herb used in ancient India with the same basic indications. They are now found in modern medicine working together in a synergistic combination.

Summary and Conclusions

The untoward side-effects of Rauwolfia and reserpine have been successfully overcome by the use of small, nontoxic doses of ephedrine in combination with the Rauwolfia or with the reserpine. The dosage of choice for the ephedrine is approximately ⅛ grain (8 mg.) per dose, that of Rauwolfia from 100 to 200 mg. of the whole powdered root per dose, and the dose of reserpine from 0.1 to 0.25 mg. per dose. Each dose is given three times daily: in the early morning, near noon, and at 4 p. m.

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PREDNISONE AND PREDNISOLONE IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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• *Prednisone and prednisolone were used in treating 31 patients with active systemic lupus erythematosus. The pattern of clinical improvement closely paralleled that obtained in previous work with corticotropin and cortisone. The fever abated in 24 to 48 hours, joint pains disappeared in several days, and pleural effusions and cutaneous lesions subsided in one to two weeks.*

The necessary dosages of these two drugs, in milligrams, are smaller than those for corticotropin and cortisone; side-effects were slower in appearing; and there was less sodium retention than with hydrocortisone. Nevertheless, when high dosages are required, a low-sodium diet is necessary in order to avoid edema and congestive heart failure and a regimen to prevent peptic ulcer must also be instituted. Two patients who received the largest doses developed sudden, severe glycosuria that was cleared up in one case by changing therapy to hydrocortisone and in the other by giving insulin.

The evident effectiveness of these two drugs, and their advantages in some situations, must be weighed against their increased ulcerogenic activity and their diabetogenic potency.

During the past five years, I have had the opportunity to treat 160 patients with systemic lupus erythematosus with corticotropin, cortisone, and the newer antiflammatory hormones and chemicals.[1] Since Bunim's report on the efficacy of prednisone and prednisolone, 31 patients have been treated with these drugs for periods ranging from one to six months.[1a] The aim of this study is to review the recent advances in steroid therapy of this disease since our last report in 1952.[1b]

Clinical Material

Thirty-one patients with active systemic lupus erythematosus were treated. The diagnoses were proved by the finding of L. E. cells in 25 cases, compatible biopsy and clinical picture in 4 patients, and compatible clinical picture alone in 2 instances. Three patients had had no previous therapy of any type, seven had received antimalarial drugs with inadequate response, and the remainder were patients maintained with varying degrees of success on corticotropin, cortisone, and hydrocortisone [1c] (table 1). There were 26 females and 5 males ranging in age from 8 to 67 years, with a median age of 30 years. The duration of their illness varied from 4 to 244 months, with a median of 38 months (table 2).

TABLE 1.—*Diagnosis and Treatment in Thirty-One Cases of Systemic Lupus Erythematosus*

	No.	%
Females	26	84
Males	5	16
Method of Diagnosis		
L. E. cells	25	80
Biopsy and clinical picture	4	13
Clinical picture alone	2	7
Treatment		
Prednisone alone	13	42
Prednisolone	9	29
Both at different times	9	29
Concurrent antimalarial therapy	11	32

Dosage

Thirteen patients were treated with prednisone alone and nine with prednisolone. Nine patients had courses of each drug, one given immediately after a maintenance dose of the other had been established. There was a total of 57.6 patient months of observation on prednisone and 30.8 months on prednisolone. Eleven individuals received antimalarial drugs concurrently, but no attempt was made to alter the dosage of these drugs. The rationale for this has been discussed elsewhere.[1c]

Since the dosage of steroid required varies with the severity of the disease, the initial doses employed were estimated according to the clinical severity of the illness. The amounts given at the onset to patients who had received no previous steroid therapy were as low as 10 mg. per day of prednisone to an 8-year-old girl whose main manifestation at the time was mild rheumatoid arthritis and as high as 40 mg. per day to a 37-year-old woman with severe pericarditis and arthritis. In both instances, the doses employed were adequate for good control. As much as 120 mg. per day of prednisone was successfully utilized to control a patient who had been inadequately helped by 480 mg. per day of hydrocortisone. One hundred sixty milligrams per day of prednisolone has controlled a patient whose illness was active despite 400 mg. of cortisone per day. These high doses have been given as long as a month. The principles involved in the use of these newer steroids are identical with those used in therapy with older agents. If there was no clinical improvement, best judged by the temperature response in 24 to 48 hours, then the dose of steroid was increased by increments of 25 to 100%, depending upon the clinical urgency of the situation, until a therapeutic response occurred. As much as 3,500 mg. of cortisone has been used per day in treating an acute exacerbation of lupus, with successful outcome. There are no fixed limits of the dosages required to produce remissions. Once the patient is afebrile, the amount of medication must not be reduced until there is general improvement in the laboratory changes as well as the clinical picture of the patient. It is advisable to continue high dosages of steroids until all the abnormal physical findings, such as pleural effusion, pericarditis with effusion, and other active evidences of

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The prednisone used in this study was supplied by Merck & Company, Inc., Rahway, N. J., and by Schering Corporation, Bloomfield, N. J., as Deltra and Meticorten. Prednisolone was also supplied, as Hydeltra and Meticortelone, by Merck & Company, Inc., and Schering Corporation.

inflammation, subside. Advanced renal disease is the one exception that will not benefit from continued high dosages.

It is no longer necessary to routinely induce overt Cushingoid changes in the first 14 days of treatment in order to reverse the pathological features as suggested in our earlier report on the use of corticotropin and cortisone. The reason for this is that the anti-inflammatory action of the newer hormones is much greater than their other hormonal effects. If a patient has neurological involvement, however, it is better to use much higher dosages than may really be necessary in order to induce an early Cushing syndrome to be certain that the maximum anti-inflammatory effect is most readily obtained.

When the hemoglobin level has become normal and abnormal physical findings have disappeared, the steroid dose is reduced, usually by decrements of about 10%. There should be waiting periods of four to seven days or longer between dosage reductions to observe signs of relapse. Mild relapse with slight return of symptoms often occurs within 24 hours, but this subsides spontaneously without dosage elevation if the disease is adequately controlled by medication. The patients have been encouraged to take salicylates frequently for minor exacerbation of aches and pains.

TABLE 2.—*Clinical Data on Thirty-One Cases of Systemic Lupus Erythematosus*

	Range	Median	Mean
Age, yr.	8-67	30	33
Duration of disease, mo.	4-244	38	60.1
Duration of all steroid treatment, mo.	½-53	11	14.8
Prednisone therapy (22 cases), mo.	¼-6	3.0	1.9
Prednisolone therapy (18 cases), mo.	½-41½	1.0	1.7
Prednisone therapeutic ratio *			
× cortisone (10 cases)	1-10	5.0	5.1
× hydrocortisone (4 cases)	2.5-4.0	4.0	3.6
× corticotropin gel (1 case)	1.3	....	....
Prednisolone therapeutic ratio			
× cortisone (6 cases)	5-6	5.0	5.2
× corticotropin gel (1 case)	3.0	....	....
Dosages, mg. per day			
Prednisone			
Initial dose † (6 cases)	10-120	22.5	46
Maintenance dose (21 cases)	5-80	22	29
Prednisolone			
Initial dose † (6 cases)	15-100	50	64
Maintenance dose (14 cases)	5-80	22.0	30

* Therapeutic ratio = amount of drug required to produce equal anti-inflammatory action on a milligram-for-milligram basis.
† Dose required to induce remission in uncontrolled patients.

Comparison of Prednisone and Prednisolone with Other Steroids and with Each Other

Table 2 lists the previous steroid therapy that controlled 22 of the patients and the ratio of prednisone or prednisolone required to maintain as good or better control. Prednisone varied from being as little as equipotent to cortisone on a milligram-for-milligram basis in one case to as much as 10 times more potent in another case. In other words, the therapeutic ratio varied from 1 to 10, the median being 5 times. The median therapeutic ratio comparing this drug to hydrocortisone was 4.0, with a variation of 2.5 to 4.0. The therapeutic ratio of prednisolone as determined in six patients seemed to have a narrower range of variability, and the median was five times. Two individuals received corticotropin gel every 12 hours, and the prednisone ratio was 1.3 times and the prednisolone ratio 3 times the total daily dose.

Six patients who were stabilized with prednisone were changed to the identical maintenance dose of prednisolone. In three patients, one of whom was entering a complete remission, there was no change in status. In the other three individuals, there was a severe relapse with recurrence of fever and arthralgia that subsided 24 hours after returning to the identical maintenance dose of prednisone that they had been receiving. One patient who was inadequately controlled with 80 mg. of prednisolone per day after five days was changed to the same dose of prednisone, and within 12 hours there was a dramatic subjective and objective improvement. Twenty of 22 patients were well controlled with prednisone. Of the two who were not, one was better controlled by 75 mg. per day of cortisone than by 50 of prednisone, and she returned to that drug; the other patient had a fulminant exacerbation of her disease refractory to 100 mg. per day of prednisone and unaffected by cortisone in increasing doses up to 1,600 mg. per day.

Prednisolone was used in 18 cases. Thirteen were well controlled and five poorly controlled. Of those poorly controlled, three patients had been receiving identical doses of prednisone, and their symptoms improved within 24 hours after returning to that drug. Another patient who had never received prednisone and was poorly controlled with 80 mg. per day of prednisolone had an overnight response on being transferred to the identical dose of prednisone. The fifth patient felt better with 100 mg. per day of cortisone than with 30 mg. per day of prednisolone.

Adjuvant Therapy

Eleven patients who were taking doses of over 40 mg. per day of prednisone or prednisolone or who had had a recent problem with congestive failure or nephropathy were placed on a low-sodium diet approximating 200 mg. per day. Contrary to the experience of others, these steroids retain sodium in the patients mentioned, particularly in those with renal or cardiac damage. Their sodium and water retention is less, however, than that of corticotropin, cortisone, and hydrocortisone.

Three patients with slight edema secondary to renal disease were transferred from hydrocortisone to prednisone; two lost their swelling, but one did not. Edema appeared in two others with cardiorenal damage, one of whom was on a constant 200-mg. sodium diet in the hospital and gained 5 lb. (2.3 kg.) with 20 mg. per day of prednisone over several days. He also gained an additional 9 lb. (4.1 kg.) with a similar dosage of prednisolone given several weeks later. In the second patient, edema appeared after discharge from the hospital when she discontinued her low-sodium diet. The swelling cleared soon after she resumed her diet. There was an additional diuresis on transfer to these steroids in eight patients within 48 hours of from 3 to 6 lb. (1.3 to 2.7 kg.), with a median of 4 lb. (1.8 kg.) and a mean of 4.5 lb. (2 kg). The weight lost in edema was usually replaced by a similar or greater over-all weight gain in most of these

patients over the course of the next few weeks, due to the appetite-stimulating effect, which is similar to that of the older steroids.

Supplementary potassium was given to only five patients who received large doses of steroids. There was no clinical or laboratory evidence of induced potassium deficiency. Twelve grams or more per day was prescribed in a liquid form, since coated tablets are often not absorbed.

The problem of ulcerogenesis with the new steroids has been well documented.[2] During the past three years we have routinely placed all patients taking over 50 mg. of cortisone per day for protracted periods on a modified regular ulcer diet, with milk and antacids between meals as well as anticholinergic drugs, usually propantheline (Pro-Banthine) bromide, 15 mg. before meals and 30 mg. upon retiring. About 100 patients with lupus have been treated in this manner, and since this time no patient who has adhered even fairly well to this regimen has developed signs or symptoms of peptic ulcer. Prior to that, several patients in our first group of 60 cases had perforated peptic ulcers without antecedent symptoms. Antacids given alone, as suggested by Bunim,[3] are insufficient protection. One patient who received antacid with milk regularly between meals and 400 mg. of cortisone per day for several months developed an acute perforated gastric ulcer. According to Bunim, 4 out of 18 patients receiving prednisone and prednisolone develop ulcers as demonstrated by x-ray, if they are on a regular diet.[2a] These heal with ulcer therapy despite continuation of the steroids. Our patients were urged to remain on an ulcer regimen until the total daily dose of prednisone or prednisolone was less than 10 mg.

Twenty-six of the 31 patients who received over 10 mg. per day of either steroid adhered fairly well to an ulcer diet, and 27 took the anticholinergic drugs prescribed. Symptoms of peptic ulcer developed in only one patient, a 25-year-old woman, who had lupus for five years and who had been receiving hormonal therapy, usually about 60 mg. per day of hydrocortisone, for four and a half years. She did not take antacids or anticholinergic drugs throughout most of this period and had some mild epigastric distress. On April 18, 1955, she was started on therapy with 30 mg. per day of prednisone along with the recommended antiulcer regimen and felt fine until the latter part of August, 1955, when, while receiving a maintenance dose of 20 mg. per day, she discontinued her ulcer regimen completely. Within several weeks, classic ulcer symptoms appeared. X-ray studies demonstrated an ulcer 1.5 cm. in diameter in the duodenum. Soon after restarting the ulcer regimen, her symptoms disappeared, despite the continuation of the same maintenance dose of steroids.

Osteoporosis with compression fractures has appeared in two ambulatory patients 12 and 14 years of age, after a year or more of high doses of cortisone, that is, over several hundred milligrams per day. With reduction in steroids and androgen therapy, their symptoms disappeared and recalcification occurred. X-rays of the thoracic and lumbar spine are taken at six-month to yearly intervals on all patients receiving the high doses. No patients have yet developed symptoms of osteoporosis while receiving prednisone or prednisolone.

Antimalarial Therapy

Since the introduction of quinacrine (Atabrine) hydrochloride for the treatment of discoid lupus and my demonstration of its value in milder cases of systemic lupus, it has continued to be utilized as adjunctive treatment, particularly in the patients who have been stabilized for months on the same dose of steroids and in whom further dosage reductions are accompanied by signs of relapse.[1c] The nonspecific anti-inflammatory action of the antimalarials has also been demonstrated in rheumatoid arthritis.[4] Twelve patients received antimalarial drugs concurrently with the newer steroids. Some patients were already receiving these agents, and no attempt was made to change their dose while receiving prednisone or prednisolone. The dosages of antimalarial drugs used in patients on steroidal therapy were usually a maximum of 0.4 gm. of atabrine per day, 0.75 gm. of chloroquine per day, or 0.6 gm. of amodiaquin (Camoquin) hydrochloride per day for months. It is too soon to evaluate their role in reduction and discontinuance of therapy with newer steroids, but the experience with their use along with the older steroidal hormones suggests that they will be valuable adjuncts.

TABLE 3.—*Side-Effects of Prednisone and Prednisolone in Thirty-One Patients*

Side-Effect		Cases
Cushingoid appearance		13
Initial development	6	
Unchanged	7	
Acne only		5
Hirsutism only		1
Striae		1
Diabetes mellitus (severe)		2
Thrombophlebitis		1
Drug tolerance		1

Side-Effects

These newer steroids have the same side-effects as the older therapeutic agents of this type. Some of these have already been discussed under adjuvant therapy above. In six patients a Cushingoid appearance developed, usually within 21 to 60 days after starting the medication with doses of 15 to 60 mg. per day of both drugs. This usually appears with cortisone in high dosages within about two weeks and with corticotropin in about 10 days or less. This appearance, once induced, persisted, since the dosage of the steroid medication has not yet been sufficiently reduced in the patients. Seven patients were rendered Cushingoid by other steroids, and their appearance remained unchanged after months of prednisone or prednisolone therapy (table 3).

Five patients had acne without other changes. One had a spontaneous thrombophlebitis. One had a neurorelapse of his disease at a time when he was apparently well controlled, and his symptoms cleared on increasing the dose of prednisolone from 10 to 40 mg. per day. In two patients, the blood pressure rose an average of 20 mm. Hg systolic to 23 diastolic. In another patient with renal changes on 80 mg. per day of prednisone, it rose from 110/70 to 150/110 several days after a low-sodium diet was discontinued.

The most significant and disturbing side-effect has been the production of severe diabetes mellitus in the two patients who received the largest doses of prednisone and prednisolone. They did not have the benign asymptomatic glycosuria that often occurs with high dosages of the other steroids with a moderately elevated blood sugar level and that subsides rapidly on reduction of the dosage of steroids without insulin.

Report of Cases

CASE 1.—A 29-year-old Mexican housewife with proved systemic lupus erythematosus of 26 months' duration had been fairly well controlled with 100 to 200 mg. per day of hydrocortisone until May, 1955, when peripheral neuropathy appeared associated with a chorea secondary to a relapse of her disease. The neurological disease was so extensive that the patient was bedridden and helpless. Medication was changed to prednisone, 120 mg. per day, on June 28. When this dose was gradually reduced during the course of the next six weeks to 70 mg. per day, her hematocrit dropped from 39 to 31 and a spontaneous thrombophlebitis appeared that responded well to anticoagulant therapy. The maintenance dose of prednisone was increased to 90 mg. per day, and, during the following three weeks, the hematocrit returned to its former value and again the steroid dose was reduced gradually to 70 mg. per day (fig. 1). Twelve weeks after

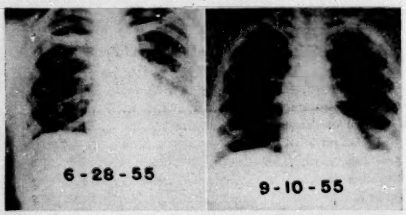

Fig. 1.—Effect of prednisone on pleuritis, pericarditis, and myocarditis of systemic lupus erythematosus. Results of two and one-half months' treatment of patient in case 1 with doses of from 120 to 70 mg. per day.

the start of prednisone treatment, while the neurological improvement had progressed sufficiently for the patient to be ambulatory in a walker and feeding herself, polydipsia, polyphagia, and polyuria suddenly appeared. Urinalysis revealed 4+ sugar and no acetone. The dose of prednisone was reduced to 20 mg. per day for the next two days, with only slight improvement in her diabetic symptoms and no relapse of her lupus. The patient was then hospitalized. At this time her blood sugar was 500 mg. per 100 cc. and carbon dioxide combining power 28 mEq. per liter. The patient was then transferred to hydrocortisone, 20 mg. four times daily, and placed on a diet containing 200 gm. per day of carbohydrate and 1,800 calories. Within 24 hours, there was less polydipsia and polyuria, and by the next day all her symptoms subsided without the use of insulin. During the week in the hospital, and for the subsequent several weeks, she has remained afebrile and asymptomatic despite the change in her medication. On discharge, the blood sugar level had fallen to 240 mg. per 100 cc. and urine sugar was 1+. Two days later, the urine became sugar-free and has remained so. There was no family history of diabetes. On June 7, 1954, prior to the institution of any therapy, the blood sugar level was 102 mg. per 100 cc. After the patient had received 240 mg. of hydrocortisone per day for two weeks, fasting blood sugar level was only 121 mg.

Comment.—This case shows two things of importance. One is the severity of the diabetes with its fulminant onset and the other is the probable appearance of tolerance to the large doses of prednisone employed.

CASE 2.—A 25-year-old Mexican woman had active systemic lupus for two years and had been receiving steroid therapy a year when, because of severe anasarca secondary to renal involvement as well as inadequate over-all control of her disease, she was given prednisolone. At this time she was markedly Cushingoid with 400 mg. of cortisone per day. In order to control her symptoms, she had to be given 160 mg. per day of prednisolone. Within two weeks polydipsia, polyphagia, and polyuria appeared. Her father, who was diabetic, checked her urine and found 4+ sugar. She was hospitalized, and her blood sugar level was found to be 1,500 mg. per 100 cc. and carbon dioxide 24 mEq. per liter. The dose of prednisolone was reduced to 80 mg. per day, and the diabetes was controlled by diet and 60 units of isophane (NPH) insulin per day. The patient's Cushingoid appearance remained despite prednisolone therapy. The diabetes was finally controlled with a maintenance dose of 30 units of isophane insulin per day along with 80 mg. of prednisolone per day.

A suggestion that tolerance to these newer steroids may become a problem was noted in one patient. The patient in case 1 required 80 mg. per day of prednisone for control for three months and relapsed when the dose was reduced. After the appearance of diabetes, the systemic lupus erythematosus was well controlled with 80 mg. per day of hydrocortisone and the diabetes disappeared.

TABLE 4.—*Laboratory Changes Produced by Prednisone and Prednisolone*

	Range	Median	Mean
Hemoglobin (change in gm.)			
Increased (16 cases)	1.0-6.0	2.5	2.8
Decreased (1 case)	1.5	...	...
No change (14 cases)	.....	...	...
White blood cell count (change in thousands)			
Increased (7 cases)	2.5	4.0	4.0
Decreased (1 case)	2.0	...	...
No change (23 cases)	.....	...	...
Sedimentation rate (Wintrobe) *			
Increased (3 cases)	8-21	15	14
Decreased (15 cases)	4-32	20	19
No change (6 cases)	.....	...	...

* Adequate data existed for 24 cases. Changes recorded as mm.

Results of Treatment

The pattern of clinical improvement closely parallels that obtained by the previous treatment with corticotropin and cortisone. The fever abates in 24 to 48 hours, joint pains disappear in several days, and pleural effusion and cutaneous lesions subside in one to two weeks. Retinal changes, anemia, adrenalopathy, and cachexia gradually improve over a period of several weeks. Renal abnormalities, including proteinuria, sediment changes, and nitrogen retention of short duration, may return to normal during remission with or without treatment. The long-standing renal lesions, however, are unaffected by steroidal treatment but seem to be helped by nitrogen mustard.[5] Six patients had nephropathy of this type, and these were unchanged by treatment. No individuals had renal involvement at the onset of treatment with these steroids, nor did any develop renal involvement while maintained on them. Table 4 gives detailed data on improvement in hemoglobin level, white blood cell count, and sedimentation rate. The sedimentation rate cannot be used as a guide to maintenance dosage because, although it tends to fall from its initial high level, it often reaches a plateau in many patients at from 30 to 45 mm. per hour (Wintrobe). Further dosage changes must be judged by the clinical picture and whether or not the

hemoglobin level is falling. Occasionally the sedimentation rate will return to normal and remain there. In this case there is usually a complete remission.

The presence of L. E. cells during treatment was adequately studied in 26 cases. They were absent in 19 cases throughout therapy. The cells persisted in one case, appeared in one individual, and disappeared in five cases in from 7 weeks to 16 weeks of treatment, an average of 10 weeks after treatment began. The finding of these cells depends to a large extent on the duration of the search for them. Thousands of white blood cells at times must be examined before a single L. E. cell is discovered. The smears were prepared by the heparin technique and studied for 10 minutes per test.[6] There is evidence that the heparin technique is less sensitive than the clot technique.[2b] Some L. E. cells may persist with more sensitive techniques; however, the number of cells greatly decreases with good treatment regardless of the technique

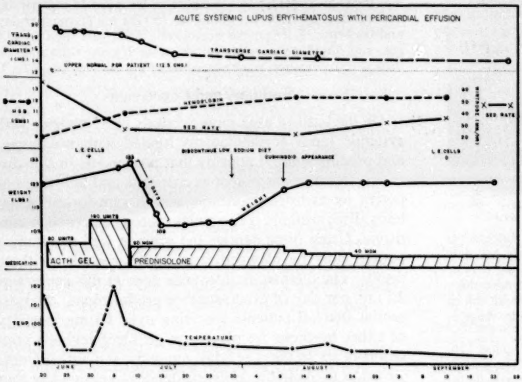

Fig. 2.—Course of patient in case 3.

of the test used. The following two cases illustrate the pattern of response that can be expected with this form of treatment.

CASE 3.—A 13-year-old Negro girl was admitted to the Los Angeles County General Hospital on June 19, 1955, complaining of puffy eyelids and fever of three weeks' duration. She had been in good health until three weeks prior to admission, when her mother noted puffy eyelids and face and ankle edema associated with pain and swelling of the proximal interphalangeal joints. The patient also complained of persistent headaches and tiredness. She often had a temperature of 104 F. On examination her temperature was 99.8 F, pulse 120 per minute, respirations 28, and blood pressure 115/40 mm. Hg. The girl was a well-developed and well-nourished acutely ill 13-year-old with periorbital edema. Subcutaneous nodules 2.5 cm. by 1 cm. in diameter were noted on the dorsum of both hands. The heart tones were poor. A soft grade 1 apical systolic murmur was present. The left border of dulness was beyond the anterior axillary line. One plus ankle edema was present.

Blood studies revealed a hemoglobin level of 9.0 gm. per 100 cc. and white blood cell count of 8,600 per cubic millimeter, with a normal differential. Wintrobe sedimentation rate was 66 mm. per hour. A sickle cell preparation was negative. Urinalysis showed 1+ albumin, with the remainder of the examination being within normal limits. Nonprotein nitrogen was 35 mg. per 100 cc., serum albumin 3.0 gm. per 100 cc., and globulin 4.2 gm. per 100 cc. Chest x-ray revealed marked globular cardiomegaly (fig. 2 and 3). The electrocardiogram was consistent with chronic pericarditis. Serologic tests for syphilis were negative.

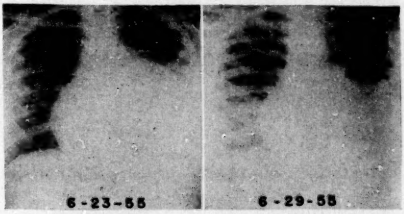

Fig. 3.—Roentgenograms of patient in case 3, showing pneumopericardium in second film and lack of change in heart size after eight days' treatment with corticotropin gel, 40 units twice daily intramuscularly.

A pericardial tap was performed and 75 cc. of serosanguineous material removed and air injected. A tentative diagnosis of rheumatic pericarditis was made, and therapy was started on June 21, 1955, with corticotropin, 40 units intramuscularly twice daily, and a 500 mg. sodium diet. During the week after admission hyperpigmented maculopapular lesions appeared only on the left cheek, varying in size from pinpoint to 0.5 cm. in diameter. They had irregular borders and a smooth, shiny appearance. Biopsy showed follicular plugging, hyperkeratosis, and inflammation. This was interpreted as being compatible with acute lupus erythematosus. L. E. cells were found in the peripheral blood at this time. Ten days after the start of corticotropin treatment, the patient's condition was unchanged and the dose was increased to 80 units twice daily. The following week her clinical condition was the same and ankle edema persisted. Corticotropin therapy was stopped and prednisolone begun in a dose of 15 mg. four times daily, with propantheline, 15 mg. before meals and 30 mg. at bedtime. The patient also received six feedings a day, with antacids between meals. Note the response illustrated in the graphic chart of her course (fig. 2) and the x-rays (fig. 3, 4, and 5).

The 23 lb. (10.4 kg.) weight loss in seven days is due not only to the decreased sodium retention caused by prednisolone as compared to corticotropin but also to the marked anti-inflammatory effects of these drugs. The appearance of initial weight loss in the acutely ill lupus patient who is placed on adequate steroid treatment is the usual finding because of the loss of inflammatory edema. On July 30, 1955, three weeks after prednisolone therapy was begun, moon face and acne appeared.

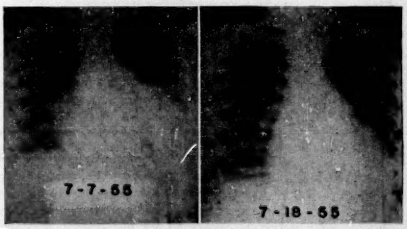

Fig. 4.—Roentgenograms of patient in case 3 taken on the day of starting prednisolone therapy, 60 mg. per day, and 11 days later, while receiving the same dose. (See also fig. 5.)

CASE 4.—A 16-year-old Negro girl was in good health until January, 1955, when acute rheumatoid arthritis appeared in her hands, wrists, and knees. Pericarditic pain also was present at this time as well as fever. The patient was hospitalized elsewhere

on Feb. 25, 1955. Laboratory studies revealed a hemolytic anemia, with 4.5 gm. per 100 cc. of hemoglobin. The white blood cell count was 11,400 per cubic millimeter, with marked anisocytosis and 4 nucleated red blood cells per high-power field. A Coombs test was negative. A biopsy of a lymph node showed hyperplasia. The patient was given three blood transfusions.

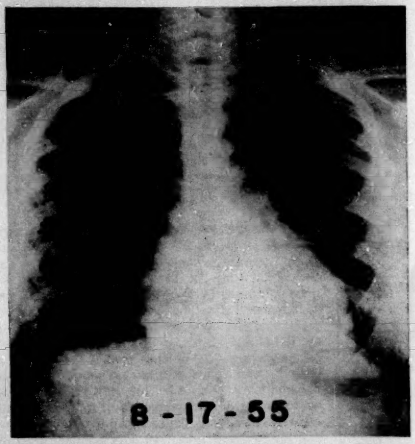

Fig. 5.—Roentgenogram of patient in case 3 taken 40 days after beginning treatment, at which time she was Cushingoid and receiving 40 mg. per day of prednisolone.

Afterward her hemoglobin level was 10.5 gm. and reticulocyte count 31.7%. She was also given cortisone, 150 mg. per day, which controlled her symptoms, but she stopped taking it after several months because of its cost. Within several weeks there was a relapse of her symptoms, and these persisted with minor remissions and exacerbations until admission to the Los Angeles County General Hospital on July 26, 1955.

On admission the patient's temperature was 101 F, pulse 110, respirations 24, and blood pressure 110/80 mm. Hg. The patient was an obese, well-developed Negro with acute fusiform dilatation of the proximal interphalangeal joints. Bilateral effusion was present in the knee joints. There was pain on motion of the neck and shoulders. Moderate cervical and axillary adenopathy was present. The remainder of the examination was within normal limits.

Laboratory studies revealed a hemoglobin level of 7.5 gm. per 100 cc. and white blood cell count of 8,400 per cubic millimeter with a normal differential. There was marked anisocytosis and spherocytosis on the smear. Occasional nucleated red blood cells were present. The reticulocyte count was 9.7%. A sickle cell preparation was negative. The serum albumin was 3.5 gm. per 100 cc. and globulin 4.5 gm. per 100 cc. A serologic test for syphilis was negative. The icteric index was 12. The thymol turbidity was 16 units and the cephalin flocculation 4+.

The patient was given prednisolone, 10 mg. three times a day after meals, methantheline, 50 mg. before meals and at bedtime, with antacids and six feedings daily without limitation of sodium intake. Within 24 hours she was asymptomatic. Within 48 hours after starting steroid therapy, she lost 3 lb. (1.3 kg.) of inflammatory edema by diuresis. On Aug. 24, 1955, the patient stopped taking prednisolone and within one day there was a relapse of symptoms with fever to 102 F. Twenty-four hours after medication was restarted, she was again asymptomatic. By Sept. 7, 1955, the hemoglobin level had risen to 13.0 gm. She was then Cushingoid, and a decrease in dosage to 25 mg. per day was advised. By error, she continued to take the 30 mg. per day, and on Sept. 28, 1955, the hemoglobin level had risen to 13.9 gm. and blood pressure to 140/95 mm. Hg. At this time the dosage of medication was reduced to 25 mg. per day (fig. 6).

Summary and Conclusions

On the basis of a six months' study of 31 patients with systemic lupus erythematosus treated with prednisone and prednisolone, it appears that prednisone in this disease is five times as potent as cortisone and four times as potent as hydrocortisone on a milligram-for-milligram basis. Prednisolone is five times more effective than cortisone. Using these figures, the average well-maintained patient may be changed from older steroids to these agents. The median maintenance dose in this series was 22 mg. per day of prednisone or prednisolone. It is essential that all patients receiving over 10 mg. per day of either hormone be placed on an ulcer regimen consisting of six feedings per day, antacids, and anticholinergic drugs to avoid the 22% incidence of peptic ulcer that occurs in patients not on an ulcer regimen. A low-sodium diet is necessary for most patients taking over 50 mg. per day of these hormones over long periods and also in all patients with significant cardiac or renal disease, to avoid edema and congestive failure. The side-effects of these newer steroids are identical with those produced by the older ones but are slower in appearing. The most significant and disturbing side-effect was the production of severe diabetes mellitus in two patients who received the largest doses of these drugs. In one case the symptoms cleared after transferring the patient to hydrocortisone therapy and in the other insulin was utilized while the patient continued to take prednisolone. Prednisone seems to be a more effective drug than prednisolone on a milligram-per-milligram basis.

The pattern of clinical improvement closely parallels that obtained by the previous treatment with corticotropin and cortisone. Renal abnormalities of short duration often return to normal, whereas those of

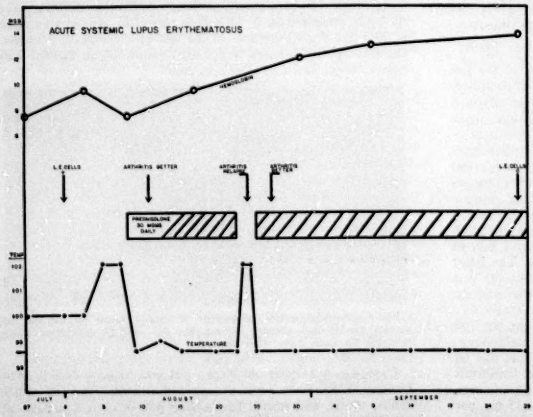

Fig. 6.—Course of patient in case 4.

long duration are unaffected by this treatment. The primary advantage of these newer steroids is that they cause slightly less sodium retention than hydrocortisone. This is helpful in treating the patient with borderline congestive failure and advanced renal disease. Against this one must weigh the increased ulcerogenic activity of these drugs as well as their diabetogenic potency.

Addendum

A total of 37 patients with systemic lupus erythematosus has been treated to date. The maximum duration of therapy is 13.5 months. Thirty-one have received courses of prednisone for a total of 169.5 patient months of observation. The mean duration of therapy is 5.5 months and the median 7.5 months. Nineteen patients received courses of prednisolone for 63 patient months of study. The mean duration of therapy was 3.3 months and the median 2.0 months. The observations reported in the study hold true for this additional experience. The maximum dose of prednisone utilized has been 240 mg. per day for a week with benefit in one of two cases.

One patient, a 62-year-old white male who had received from 25 to 15 mg. of prednisone daily for five months, developed classic peptic ulcer symptoms despite being on the recommended regimen. The dose of prednisone was reduced to 10 mg. daily, and the dose of propantheline bromide was increased to 120 mg. daily. Within one week his symptoms disappeared and he has not had a recurrence during the past five months. Boland [7] showed the incidence of gastric complaints in patients receiving an average maintenance dose of 12.9 mg. of prednisone or prednisolone per day to be 37% in a group of 70 rheumatoid arthritics not on an ulcer regimen. This confirms the importance of a routine ulcer schedule for all patients taking over 10 mg. per day of these steroids.

Since the incidence of spontaneous remission in systemic lupus erythematosus is 40% or more, I do not initially start every patient on steroid therapy. Bed rest and salicylates to the point of intoxication are utilized initially in the milder cases. If cutaneous lesions are present or if there is no response to more conservative measures, then antimalarials are employed. If the patient is seriously ill, has renal or neurological involvement, or the illness progresses, then steroids are employed.

A third patient developed severe diabetes after seven weeks of prednisone therapy in doses up to 240 mg. per day. Her blood sugar level was 212 mg. per 100 cc., with a carbon dioxide–combining power of 28 mEq. per liter. She was transferred to therapy with hydrocortisone, 800 mg. daily, but there was no improvement in the diabetes. One week later, micrococcic pneumonia appeared. Despite antibiotic and insulin therapy, she died from pneumonitis. Preterminally for the first time the carbon dioxide–combining power fell to 10 mEq.

Gamma globulin may be of value in treating severe infections. Two other patients, who had been maintained on steroids five years and three years respectively, had infections occur while on hydrocortisone and cortisone therapy. One had a spreading cellulitis involving over one half the face that was unresponsive to four days of vigorous antibiotic therapy. Twelve hours after the patient received 30 cc. of immune globulin intramuscularly, the cellulitis stopped spreading and began to regress. This patient received another 30-cc. dose and made an uneventful recovery. The second patient had a peritoneal abscess postoperatively and developed intestinal obstruction. At the time of reoperation she received 50 cc. of immune globulin in one dose and convalesced rapidly. The rationale of the use of gamma globulin was provided by a previous study of three patients with systemic lupus erythematosus maintained at the Cushingoid level who had been given typhoid and paratyphoid vaccine without any antibody response.

Quantitative studies of the L. E. cells after treatment have been performed in a group of 54 patients treated for at least two months as outlined in this study. Utilizing a battery of three types of L. E. tests performed simultaneously, no cells were found in 23 cases and a very rare one was found in 8 additional cases.

Recent analysis of this series showed over-all results of the therapy of this disease as outlined above to be good. Of 59 untreated or inadequately treated patients, 50% died 24 months after onset of symptoms; of 138 adequately treated, ill for 24 months or longer, less than 10% have died. This is a significant difference.

1200 N. State St. (33).

1. (*a*) Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis, J. A. M. A. **157**: 311-318 (Jan. 22) 1955. (*b*) Dubois, E. L., and others: Corticotropin and Cortisone Treatment for Systemic Lupus Erythematosus, ibid. **149**: 995-1002 (July 12) 1952. (*c*) Dubois, E. L.: Quinacrine (Atabrine) in Treatment of Systemic and Discoid Lupus Erythematosus, A. M. A. Arch. Int. Med. **94**: 131-141 (July) 1954.

2. (*a*) Black, R. L.; Bollet, A. J.; Segal, S., and Bunim, J. J.: Observations on Prolonged Administration of Metacortandracin in Rheumatoid Arthritis, read before the American Rheumatism Association, Atlantic City, N. J., June 3, 1955. (*b*) Zimmer, F. E., and Hargraves, M. M.: The Effect of Blood Coagulation on L. E. Cell Formation, Proc. Staff. Meet. Mayo Clin. **27**: 424-430 (Oct. 22) 1952.

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4. Freedman, A., and Bach, F.: Mepacrine and Rheumatoid Arthritis, Lancet **2**: 321 (Aug. 16) 1952.

5. Dubois, E. L.: Nitrogen Mustard in the Treatment of Systemic Lupus Erythematosus, A. M. A. Arch. Int. Med. **93**: 667-672 (May) 1954.

6. Dubois, E. L.: A Simplified Method for L. E. Cell Test: Results of a 3 Year Study of 700 Tests in Many Disease States, A. M. A. Arch. Int. Med. **92**: 168-184 (Aug.) 1953.

7. Boland, E. W.: Prednisone and Prednisolone Therapy in Rheumatoid Arthritis: Clinical Evaluation Based on Continuous Observations for Periods of Six to Nine Months, J. A. M. A. **160**: 613-621 (Feb. 25) 1956.

Stress.—Gastrointestinal ulceration with hemorrhage or perforation is an integral part of the alarm reaction of the General Adaptation Syndrome in response to a number of systemic stress factors. The repeated administration of ACTH simulates stress, in part, since it induces many of the same responses. An injection of ACTH or a stress (rage, fear, pain, a surgical procedure) may produce an increase in the excretion of adrenal corticoids in the urine and a decrease in the circulating eosinophiles in the blood. During an air raid, for example, these effects, produced by fear and anxiety, are similar to those induced by an injection of ACTH. Repeated air raids or repeated injections of ACTH may produce peptic ulcer, and during the air raids in England and other countries in the late war, there was a significant increase in the incidence of peptic ulcer, often with hemorrhage or perforation. These two mechanisms (stress and ACTH) appear to work in the same manner, since the adrenal steroids may induce epigastric pain and cause reactivation, perforation or hemorrhage of preexisting peptic ulcer or new formation of ulcer.—S. J. Gray, M.D., Stress, Hormones and Peptic Ulcer, Clinical Conference of the Chicago Medical Society, March 1-4, 1955.

CLINICAL NOTES

FATAL HEART ATTACK AND SUCCESSFUL DEFIBRILLATION

NEW CONCEPTS IN CORONARY ARTERY DISEASE

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Elden C. Weckesser, M.D.
and
Frank M. Barry, M.D., Cleveland

This is the report of a man who died from a heart attack and in whom defibrillation was successfully accomplished. He was dressed in his street clothes when death and resuscitation occurred. This probably is the first case on record of a man being rescued from a heart attack that occurred outside the operating room; we would like to receive information concerning any other similar instances. One of us (C. S. B.) successfully resuscitated a man whose heart went into asystole while he was being prepared for a gallbladder operation, but this occurred in the operating room, where all necessary equipment for resuscitation was available. This man had coronary artery disease. Another patient developed ventricular fibrillation twice during an operation for coronary artery disease. Defibrillation was successfully accomplished, but fibrillation occurred again two days after operation and the patient died. An x-ray technician died while developing a film in a Chicago hospital. Dr. C. David Brown exposed the heart and found that it was in asystole until he began to empty it by hand, and then fibrillation occurred. This patient was successfully resuscitated. He had Wolff-Parkinson-White syndrome. This case has not been reported. This man was in his street clothes but was in the hospital. Not long ago surgeons developed the resuscitation procedure for use in the operating room. Application of this method is now almost routine, and the surgeon is expected to carry it out. Courses in this subject have been established, and teaching of resuscitation has become a part of medical and surgical training programs. Now it appears that the resuscitation procedure has application beyond the operating room, perhaps even beyond the hospital, and, if so, this is a new medical project for development.

Report of a Case

This patient is a physician engaged in active practice of medicine and is 65 years of age. For many months he had indigestion, which was relieved by food, water, and antacids. On the night of June 21, 1955, he had precordial distress, which was not relieved by these measures. This distress was persistent, not severe, and not very different from previous symptoms, but he made the diagnosis of angina pectoris. At 11:30 a. m., June 22, he had an electrocardiogram made at University Hospitals. This record was consistent with early posterolateral myocardial infarction (fig. 1). At 12:55 p. m. he collapsed while leaving the hospital and fell to the floor. At 12:57 he was taken to the emergency operating room, which was nearby. He was cyanosed and had no pulse and no respirations. These procedures were done: artificial respiration, oxygen given through a face mask, and heart punctured with a needle. There were no heart sounds. The man was dead. At 12:59 the chest was slit open between the fourth and fifth ribs and the cartilages of these ribs were cut. There was no bleeding. At 1 p.m. a hand was placed beneath the heart and the heart was squeezed intermittently against the sternum. Time was not taken to open the pericardium, but it was obvious that fibrillation was occurring in the ventricles. At 1:03 the face mask was replaced by an intratracheal tube. The lungs were well oxygenated and the color of the skin improved. The patient took an occasional respiration on his own. At 1:05 the heart was shocked. Fibrillation continued in the ventricles. The heart was rhythmically emptied by hand. At 1:08 a second unsuccessful shock was given. The oxygen system was well maintained while time was taken to bring in a sterile field. A self-retaining retractor was placed in the incision, and

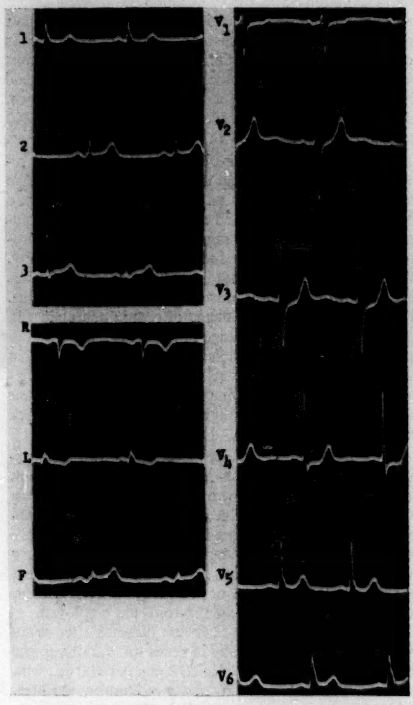

Fig. 1.—Electrocardiogram taken on the morning of June 22, 1955, about one week after the onset of anginal pain. This record is consistent with early posterolateral myocardial infarction.

this relieved pressure on the wrist while the heart was being emptied. A shoe and a sock were removed from the patient, and a needle placed in a vein for intravenous administration of fluid. The pericardium was opened. The ventricles showed coarse fibrillation. Two additional shocks were not successful. Insufficient current entered the heart because the electrodes were wrapped with gauze and the gauze was dry. They were wet with isotonic sodium chloride solution. The next shock at 1:25 delivered 3 amperes through the heart for two seconds. The fibrillation stopped and the heart began to beat. Lanatoside C (Cedilanid), a digitalis preparation, was given intravenously. Beads of perspiration appeared on the forehead of the patient as life was restored. The pulse and blood pressure were normal and

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remained normal. The blood vessels in the chest wall were ligated. A tube was placed in the chest, and the chest was closed. The patient was transferred to a surgical ward, placed in an oxygen tent, and given antibiotics. An electrocardiogram was taken at 1:37 (fig. 2).

At 8:00 a. m., June 23, the patient made a few conscious responses but did not talk. At noon he spoke some words. The systolic blood pressure varied from 100 to 130 mm. Hg, and the pulse rate was 80 to 100 per minute. On June 24, he talked and moved his extremities but had no memory of events going back several hours prior to 11:30, June 22. June 24 and 25 he showed periods of disorientation, confusion, and excitement. He was restrained and given sedation. He improved, and by June 29 he was cheerful, well-oriented, and normal. He was discharged from the hospital after a total stay of 11 days. An electrocardiogram taken July 5 is shown in figure 3. The medial end of his wound became infected, and this was opened July 11. Subsequently some infected cartilage was removed, and the wound healed satisfactorily. At the present time the patient feels strong enough to return to his medical practice. The only deficit that he has is an absence of memory of a period of 36 hours.

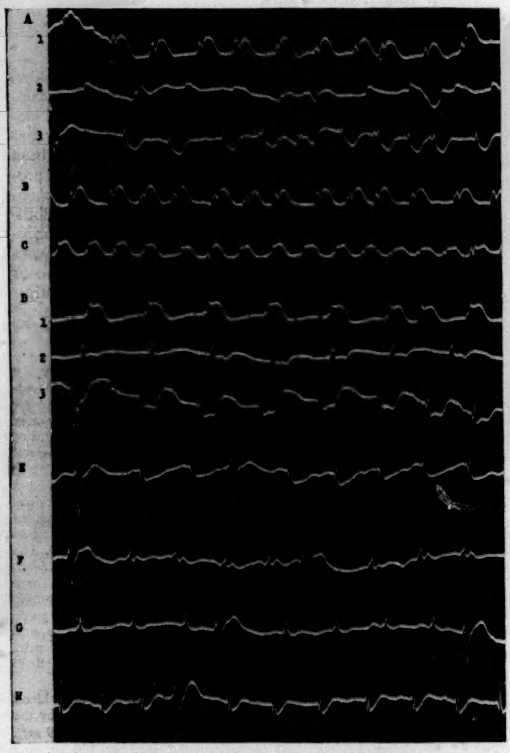

Fig. 2.—Serial recordings begun at 1:37 p. m., just after defibrillation when the heart had resumed a spontaneous beat. *A*, leads 1, 2, and 3, showing pattern of acute anterior wall infarction. Auricular fibrillation is present. *B* and *C*, lead 1 at 1:40 and 1:42; there is little change. *D*, five minutes after the administration of 0.8 mg. of lanatoside C. The ventricular rate is slower; pattern of anterior infarction persists. *E*, lead 3 at 1:54. At 1:56, *F*, there is prolonged intraventricular conduction time with occasional ventricular premature beats. At 1:59, *G*, fairly normal ventricular complexes are present with occasional ventricular premature beats. At 2:30, *H*, increased intraventricular conduction time. S-T segment depression is present.

Death Factor

The death factor in coronary artery disease is often small and reversible. It is comparable to turning the ignition switch in an automobile or to stopping and starting the pendulum of a clock. The heart wants to beat, and often it needs only a second chance. These statements have scientific support. Coronary artery disease kills in one of two ways. The vast majority of deaths, about 90% of the total, are due to electrical instability. In the remaining 10% death is due to muscle failure in hearts that remain electrically stable from one bout of coronary artery occlusion to another. Both electrical instability and muscle damage are related to oxygen content in muscle, but otherwise they are different. Electrical instability kills one-third of all the victims of this disease without muscle damage, and in the remainder the muscle destruction is not so great but that the heart could keep on beating. In the patient reported here, the heart, while it had an infarct, only needed another chance. Electrical currents are produced in the heart by differences in oxygen content in contiguous areas of muscle. They are not produced by lack of oxygen; a uniformly cyanosed heart is electrically stable. They are produced by oxygen differentials in muscle. It is these currents that kill most people with coronary artery disease.

Future Application

Resuscitation is indicated in those victims of coronary artery disease who die from electrical instability. Resuscitation is feasible when the victim dies in the hospital, provided supplies and personnel trained in resuscitation methods are available as soon as the patient dies. Preparation for resuscitation must be made before death occurs. It is suggested that trained resuscitation teams take over when a patient dies from an acute heart attack. No doubt some lives will be saved by such action. When death occurs on the golf course, in the office, or in the home, resuscitation cannot be done unless equipment and trained personnel are immediately available. These problems are not insurmountable. Any intelligent man or woman can be taught to do resuscitation. A medical or nursing degree is not a prerequisite to learn resuscitation, nor is it impossible to provide resuscitation kits to be opened for the emergency; these could be located in selected areas and be serviced whenever necessary. The veil of mystery is being lifted from heart conditions, and the dead are being brought back to life.

Summary

A physician dressed in his street clothes died from a heart attack while leaving the hospital. He was successfully resuscitated. This one experience indicates that resuscitation from fatal heart attack is not impossible and might be applied to those who die in the hospital and perhaps also to those who die outside the hospital.

Addendum

Since the preparation of this report, an almost identical case has been reported by Reagan, Young, and Nicholson.[1] Their patient developed electrical instability of the heart while a cardiogram was being taken in the emergency ward. The mechanism changed from normal

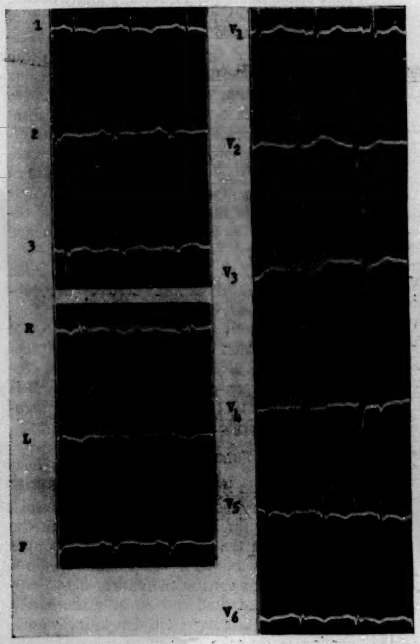

Fig. 3.—Complete electrocardiogram taken on July 5 shows evolution of a lateral wall myocardial infarct.

sinus rhythm to ventricular tachycardia to ventricular fibrillation. This patient was successfully resuscitated on April 13, 1953; this is therefore the first case in which successful fibrillation has been performed outside of the operating room.

2065 Adelbert Rd. (6) (Dr. Beck).

1. Reagan, L. B.; Young, K. R., and Nicholson, J. W.: Ventricular Defibrillation in Patient with Probable Acute Coronary Occlusion, Surgery 39:482-486 (March) 1956.

Medical History.—The value of medical history as a cultural subject is considerable, but there are other—and equally significant—functions, which should make it indispensable in a well-rounded medical curriculum. Actually, to non-physicians it must appear surprising that of all professions medicine can be taught without a firm basis of its historical development. Philosophers, even if they specialize in 20th century existentialism, are required to be familiar with the thoughts of earlier thinkers in order to grasp the full meaning of their own philosophical persuasion.—Ilza Veith, The Function and Place of the History of Medicine in Medical Education, *The Journal of Medical Education*, May, 1956.

PROLONGED HYPOTENSION WITH FATAL TERMINATION AFTER A PHENTOLAMINE (REGITINE) METHANESULFONATE TEST

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Since the introduction of the phentolamine (Regitine) methanesulfonate test [1] for the diagnosis of pheochromocytoma, it has generally been regarded as a safe and reasonably accurate procedure. No reports of fatality after its use in patients with pheochromocytoma have been found in the literature, although there are reports of prolonged hypotension with its use during surgery for pheochromocytoma [2] and of one death from ventricular fibrillation after the test in a patient without pheochromocytoma.[3] This report describes a prolonged period of hypotension, cardiac arrhythmia, and death after intravenous administration of 5 mg. of phentolamine to a patient shown to have a pheochromocytoma at autopsy.

Report of a Case

The patient, a 65-year-old woman, was admitted to the hospital on July 9, 1955, because of "weak spells and convulsions" that appeared one year before admission. The spells were characterized by palpitation, nervousness, cold and clammy hands, profuse perspiration, and then the sudden appearance of weakness and nausea followed by a grand mal seizure. Several of the episodes had occurred while the patient was straining to defecate. There had been heat intolerance, weakness, and a weight loss of approximately 18 lb. (8.2 kg.) during the previous year. Physical examination revealed a placid, well-nourished woman whose blood pressure was 150/80 mm. Hg, pulse rate 92 beats per minute, and temperature 99.6 F (37.55 C). The optic fundi revealed early arteriosclerotic changes. A 1.5-cm. soft nodule was palpated in the right lobe of the thyroid. There was a suprasternal pulsation and an apical cardiac systolic thrill. The aortic second sound was accentuated. A harsh, grade 3 apical systolic murmur was transmitted to the left axilla, and a grade 2 aortic systolic murmur was transmitted to the neck vessels. During hospitalization the heart murmurs and thrill disappeared.

Laboratory examination revealed normal urine and blood pictures. The sedimentation rate was 31 mm. per hour by the Westergren method. The fasting blood sugar level was 119 mg., calcium 9.6 mg., and phosphorus 3.2 mg. per 100 cc. The alkaline phosphatase level was 11.4 King-Armstrong units, and the cholesterol level was 310 mg. per 100 cc. The basal metabolic rate, protein-bound iodine level, serologic test for syphilis, and spinal fluid examination were all within normal limits. An electrocardiogram revealed nonspecific T-wave changes. A chest x-ray showed the heart to be slightly enlarged to the left with prominence of the aortic knob; the skull films demonstrated a moderate degree of hyperostosis frontalis interna. There were a few plaques of calcium in the vessels forming the circle of Willis. Electroencephalographic findings were normal. No central nervous system disease was demonstrated, and, since no attacks were observed during hospitalization, it was assumed that the patient's spells were probably due to recurrent paroxysmal cardiac arrhythmia with resulting cerebral ischemia. She was discharged on July 16, on a regimen of 250 mg. of procainamide hydrochloride four times daily and 30 mg. of mephobarbital three times daily.

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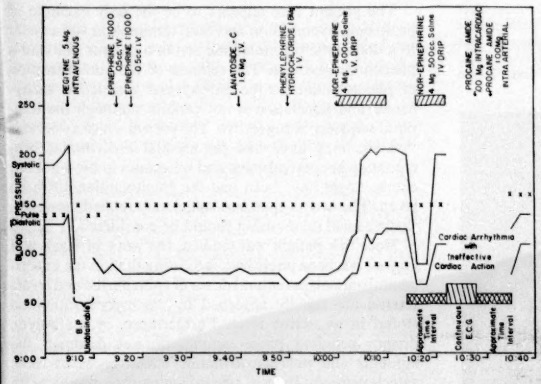

Fig. 1.—Patient's course after administration of phentolamine (Regitine) methanesulfonate.

Two weeks after discharge, the patient had another attack of vague abdominal discomfort, palpitation, and tachycardia. When she was seen by her local physician, her blood pressure was 230/130 mm. Hg and the pulse rate was 160 per minute, regular, and unaffected by carotid sinus massage. Hospitalization was advised. On admission, 24 hours later, she complained of nervousness and increased warmth. There was nausea followed by emesis of recently ingested orange juice. On physical examination, she was pale, cold, and clammy and appeared acutely ill. The blood pressure was 220/140 mm. Hg, and the pulse rate was 150 per minute and regular. No significant murmurs were present. Electrocardiography revealed a sinus tachycardia with some depression of the RS-T segments. There was no glycosuria.

A clinical diagnosis of pheochromocytoma was made, and a phentolamine test was performed to confirm this diagnosis. After the intravenous administration of 5 mg. of phentolamine, there was an immediate drop in the blood pressure from 200/130 to 90/60 mm. Hg. There was further emesis, and the patient became unresponsive. The blood pressure, as indicated in figure 1, continued to fall. Fifteen minutes after the injection of phentolamine, because of the marked hypotension and coma, 0.5 cc. of a 1:1,000 solution of epinephrine was slowly given intravenously; this was repeated in three minutes without response. The patient was given 1.6 mg. of lanatoside C (Cedilanid) intravenously and, shortly thereafter, 1.8 mg. of phenylephrine hydrochloride, which also failed to produce improvement.

Fifty-five minutes after the injection of phentolamine, intravenous administration of 4 mg. of levarterenol (*l*-norepinephrine) bitartrate in 500 cc. of isotonic sodium chloride solution was started, and continuous electrocardiographic tracings were recorded. After a slow initial response, the blood pressure rose rapidly to 200/120 mm. Hg and the pulse rate fell to 90 beats per minute from the previous rate of 150 per minute. Since the emergency appeared to be over, the levarterenol administration was slowed and then stopped. Hypotension recurred almost immediately, but when administration of the levarterenol was started again, there was an increase in the blood pressure and a return of the sinus tachycardia, which soon converted to ventricular tachycardia followed by ventricular fibrillation, loss of consciousness, a grand mal convulsion, and coma. One hundred milligrams of procainamide was injected into the heart followed by 100 mg. into the right femoral artery, and the administration of levarterenol was discontinued. During the ensuing 8 minutes there were periods of ventricular tachycardia and fibrillation (fig. 2). Although the coma persisted and the pupils became dilated, the pupils reacted to light and the Babinski reflexes were absent. The cardiac rhythm finally reverted to a supraventricular tachycardia, and the blood pressure stabilized and remained throughout the night at 140/110 mm. Hg, with a pulse rate of 160 beats per minute.

The next morning the patient appeared worse, with deepening coma. Respirations were 64 per minute and shallow. The blood pressure was 120/90 mm. Hg, pulse rate 140, and temperature 107.2 F (41.77 C). An electrocardiogram showed no change, and a chest x-ray revealed a small apical pneumothorax on the left side that was undoubtedly produced during the intracardiac injection. An hour later there was a fall in blood pressure to 88/70 mm. Hg, and 4 mg. of levarterenol in 1,000 cc. of sodium chloride solution was administered slowly. Although the blood pressure increased to 102/70 mm. Hg, the patient's condition became worse, with progressive respiratory failure, and she was pronounced dead 30½ hours after the phentolamine test.

The most significant finding at autopsy was a firm, pink, discrete spherical tumor mass 4 cm. in diameter (fig. 3) in the medulla of the right adrenal gland. On microscopic examination (fig. 4), the cells of this tumor were found to have an acinar arrangement, and the presence of chromaffin granules confirmed the diagnosis of pheochromocytoma. The left adrenal gland was normal. Secondary autopsy findings were as follows: In the heart, a few atherosclerotic plaques were present in the aortic valve and the mitral valve was thickened. There were dilatation and hypertrophy of the left ventricle and diffuse myocardial fibrosis. The coronary arteries were patent. Both lungs were

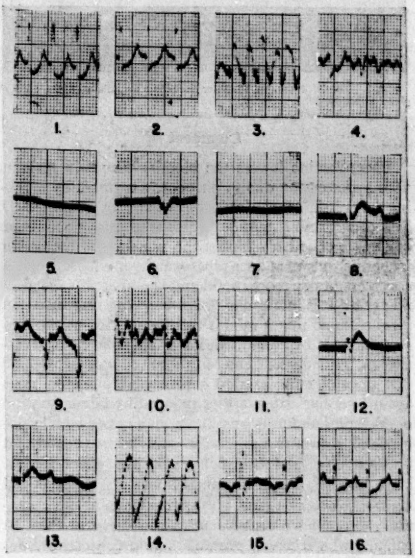

Fig. 2.—Electrocardiographic tracings made immediately before and after administration of levarterenol (*l*-norepinephrine) bitartrate. (1) supraventricular tachycardia; (2) administration of levarterenol; (3) ventricular tachycardia (lasting 12 seconds); (4) ventricular fibrillation (lasting 2 minutes, 40 seconds); (5) cardiac arrest (lasting 17 seconds); (6) idioventricular beats (lasting 29 seconds); (7) cardiac arrest (lasting 21 seconds); (8) wandering pacemaker (lasting 53 seconds); (9) tachycardia with conduction defect (lasting 36 seconds). Over the next eight minutes (approximately) the arrhythmias were (10) ventricular fibrillation; (11) cardiac arrest; (12) idioventricular beats; (13) wandering pacemaker; (14) ventricular tachycardia; (15) ectopic auricular rhythm with tachycardia; (16) supraventricular tachycardia. Levarterenol withdrawn between (4) and (5); intracardiac injection of 100 mg. of procainamide between (10) and (11); intra-arterial injection of procainamide between (12) and (13).

collapsed and almost airless. There was a 1-cm. superficial ulcer in the pylorus of the stomach. A homogeneous eosinophilic material lay between Bowman's capsule and the glomerular tuft in approximately 10% of the glomeruli. Congestion, edema, and capillary hemorrhages, thought to be agonal, were noted in the pons.

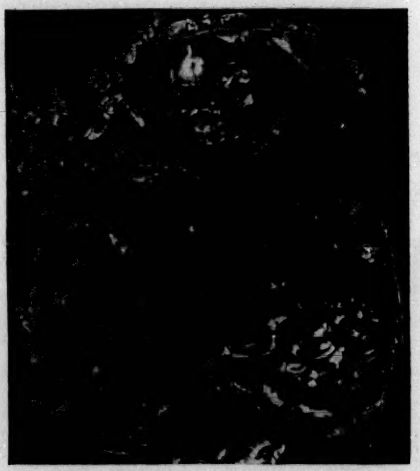

Fig. 3.—Tumor 4 cm. in diameter found in medulla of right adrenal gland at autopsy.

Comment

Phentolamine lowers the blood pressure in patients with hypertension due to pheochromocytoma by blocking the pressor effect of epinephrine and/or levarterenol.[3] The drug exhibits adrenolytic as well as sympatholytic effects. It effectively blocks the pressor substances for longer periods than does piperoxan hydrochloride and is considered to be more useful and less toxic as a diagnostic agent.[4] It is interesting that it has been suggested that phentolamine might inhibit the appearance of arrhythmias induced by administration of epinephrine or levarterenol.[5] Leimdorfer [5] and Morris and co-workers [6] found that phentolamine exerted a protective action in dogs against cardiac irregularities induced by administration of epinephrine during anesthesia maintained with cyclopropane. However, in the same study Morris found that phentolamine had no such protective effect in humans. Indeed, one of his patients who was anesthetized with cyclopropane and given phentolamine preoperatively developed a ventricular tachycardia, and 19 of 30 patients who received phentolamine preoperatively developed a sinus tachycardia, as compared with 7 of 28 patients in the control group. Moyer and Caplovitz [7] reported the occurrence of multifocal premature ventricular contractions after the use of phentolamine. Ross [3] reported a false-positive reaction to the phentolamine test in a woman with a history of paroxysmal hypertension. The test produced hypotension followed by ventricular tachycardia and fibrillation, but no pheochromocytoma was demonstrated at autopsy.

The present case appears to be the only example of prolonged hypotension and fatal termination subsequent to a diagnostic phentolamine test in a patient who had a pheochromocytoma. The relation of the administration of phentolamine to the paroxysmal ventricular tachycardia and fibrillation is not certain, although the temporal sequence is suggestive. The patient's history reveals that she may have had paroxysmal arrhythmias precipitating her convulsions, and we cannot know what her course might have been had the phentolamine not been given. The events appeared sufficiently related, however, that a causal relationship should be considered.

Since this patient was studied, the work of Raab and Gigee [8] has been published, indicating that, in the experimental animal, parenteral doses of epinephrine and levarterenol are rapidly absorbed by the myocardium and stored in an active form. Furthermore, sympatholytic drugs, including phentolamine, do not diminish the amounts and pharmacodynamic effectiveness of these catecholamines; indeed, phentolamine even produces an increase in the amounts of epinephrine and levarterenol in the myocardium. These authors feel that their findings explain the relative therapeutic inefficacy of sympatholytic drugs in such cardiac disorders as the tachycardias and the anginal syndrome. If this can be applied to man,

Fig. 4.—Photomicrograph of cells from adrenal tumor (× 800). Note acinar arrangement of cells and presence of chromaffin granules, which confirm the diagnosis of pheochromocytoma.

and if the present patient had experienced paroxysmal arrhythmia in the past as a result of a high level of catecholamines in the myocardium, the therapeutic paradox of treatment of phentolamine-induced hypotension with levarterenol is apparent.

Summary

In a 65-year-old woman with a proved pheochromocytoma, a routine phentolamine (Regitine) methanesul-

fonate test resulted in a prolonged period of hypotension that responded to administration of levarterenol (*l*-norepinephrine) bitartrate but terminated in ventricular tachycardia, ventricular fibrillation, and cardiac arrest. Although there was cardiovascular recovery from the cardiac arrest, the central nervous system did not recover, and death ensued 30½ hours after the phentolamine test.

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Varicose Veins of Pregnancy.—The superficial varicose veins of the lower extremities complicating pregnancy, which have been identified universally as classical superficial saphenous varicosities, were found to consist of two well-differentiated venous disorders. One is the mentioned saphenous varix. The other, which is limited to the pregnant state, had not been described previously and has been termed "angiectid" by us. The angiectid was present in 10% of a group of clinic patients and was nine times more frequent than the saphenous varicosity. Many controversies have been due to the past failure to recognize the angiectid, which differs markedly from the saphenous varicosity. There is no resemblance between the well-known long, cordlike, subcutaneous saphenous varix and the angiectid, which is a small, intradermal, raised, sharply circumscribed mass of bluish vessels. The saphenous varix occasions fatigue and heaviness of the leg, which contrasts sharply with the pain and resultant disability that the angiectid causes in most cases.

In contrast to the saphenous varix, many clinical features of the angiectid indicated that an imbalance of estrogen and progesterone may be a factor in the formation of the angiectid. Hormone assays in 21 patients with angiectids demonstrated normal amounts of serum chorionic gonadotropin and urinary 17-ketosteroids and variations in the titers of serum estrogen and urinary pregnanediol. The six women with symptomless angiectids had consistently low normal amounts of estrogen and pregnanediol. Of the 15 patients with painful, disabling angiectids, 14 had subnormal amounts of estrogen and/or pregnanediol. Severe pain and marked changes in the angiectid were associated with the lowest subnormal estrogen levels. The results of the hormone assays in four patients with saphenous varices were normal. Pain and disability due to the angiectids disappeared in each of the 15 patients with the use of orally administered female sex hormones. Diethylstilbestrol alone was effective in 13 cases.—P. H. Fried, M.D., P. K. Perilstein, M.D., and F. B. Wagner Jr., M.D., The Hormonal Cause of the So-Called Varicose Veins of Pregnancy, *A. M. A. Archives of Surgery*, February, 1956.

NEUROMUSCULAR PERFORMANCE AND SENSORY RECEPTIVITY IN A TRIPLE CONGENITAL AMPUTEE

REPORT OF A CASE

Ernst Jokl, M.D., Lexington, Ky.
Henry H. Kessler, M.D., West Orange, N. J.
and
Erwin W. Straus, M.D., Lexington, Ky.

This report of a 22-year-old man, born without lower arms and hands and without the distal end of the right leg, supports Adrian's observation that "The nervous system reacts to relations between stimuli and performs the appropriate task with any part of the motor system that is available. We cannot represent it as a series of machines for operating on the map of events unless we add a number of devices to make good this fundamental difference. On the sensory side there must be something to abstract the significant elements of a pattern and on the motor side something to do just the reverse, to convert the abstraction into a concrete movement."[1]

The patient, when standing, carries his weight on the left lower extremity and on the right lower extremity prosthesis. X-rays reveal an abnormal skeletal structure of the left foot (figure, *A*). Despite his multiple deformity, this patient, who is intelligent and emotionally well-balanced, was able to attain a remarkably high level of physical fitness and efficiency after a prolonged period of rehabilitation training. He stands and walks firmly, catches and throws a heavy medicine ball, and is able to swim (figure, *B*) with the aid of fins that Lorenzen [2] introduced into exercise therapy. He plays croquet (figure, *C*) and table tennis (figure, *E*) and takes part in calisthenics. He fences well, dresses without aid, and uses table implements skillfully. He is able to write by grasping the pen between the upper extremity stumps or by affixing the pen in the closed steel hooks of his hand prosthesis. He can use either the right or left prosthesis, and his handwriting is excellent (figure, *D*).

The patient was taught to play the piano (figure, *F*); rubber tips were attached to the metal ends of the hand prostheses to buffer the impact of the prostheses on the keys. By carefully selecting suitable compositions and transcriptions, he has been able to make music an important part of his life. For example, he plays the upper lead of Hambourg's transcription of a Bach cantata for three hands; the theme and harmonizations are played by the accompanist.

The motor and sensory functions of the hands are projected into the patient's arm stumps. He is able to execute highly differentiated motor tasks despite the fact that 28 of the normal 29 bones of the upper extremities, 41 of the normal complement of 44 muscles, and more than 95% of the peripheral sense receptors are absent. An experiment revealed the extent to which the sensory system of the patient adapted itself to his physical disability. With eyes closed, the patient could distinguish among wooden, metal, rubber, and woolen surfaces that he "felt" with the steel prostheses. The transfer of these contacts upon his sensory receptors took place along the cutaneous areas of attachment of the artificial limbs to the arm stumps. This young man's high level of physical efficiency presupposed the presence of a functionally efficient autonomic system, an assumption supported by an acceleration ballistocardiogram taken from across the left lower leg to the right lower extremity prosthesis (figure, *G*). In

From the Kentucky Rehabilitation Center, Inc., at the University of Kentucky (Dr. Jokl), Kessler Institute for Rehabilitation (Dr. Kessler), and Veterans Administration Hospital (Dr. Straus).

The Division of Vocational Rehabilitation of the Department of Education of the State of Kentucky, Frankfort, collaborated in this case study.

the Arbeit and Jokl classification [3] the tracing would be considered grade 1 because of the repetitiveness and congruity of the complexes.

Straus [4] points out that human posture and motion cannot be described simply by kinetically defined variants of body constellations in space and time. In human posture and motion, moral patterns and qualities of character may manifest themselves in a unique manner. The physical attainments of this patient are due to his steadfast personality, his high intelligence, and his strong motivation. In May, 1955, he received the degree of bachelor of laws and is now a practicing attorney.

53 Lincoln Park, Newark 2, N. J. (Dr. Kessler).

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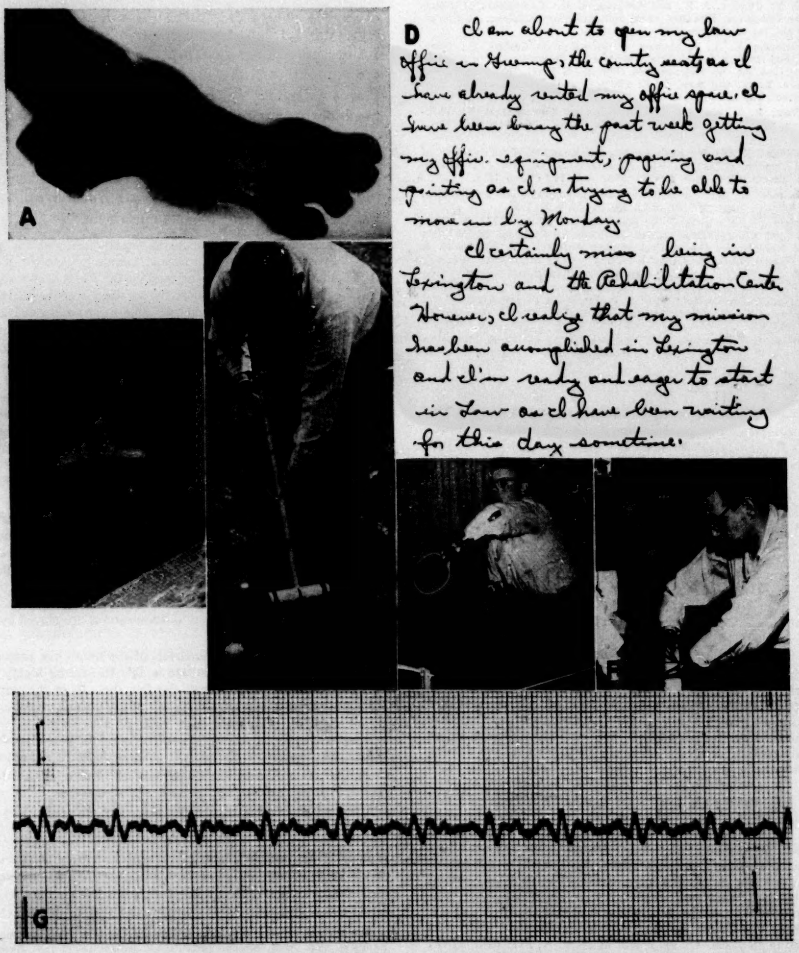
A
D
I am about to open my law office in Krum, the county seat as I have already rented my office space. I have been doing the past week getting my office equipment, papering and painting as I am trying to be able to move in by Monday.
I certainly miss being in Lexington and the Rehabilitation Center however, I realize that my mission has been accomplished in Lexington and I'm ready and eager to start in Law as I have been waiting for this day sometime.
G

A, x-rays of the left foot showing presence of four metatarsal bones and four phalanges. The great toe and first metatarsal bone are absent. The cuboid bone and the calcaneus are fused, and there is fusion between talus and calcaneus. The first and second cuneiform bones are absent. *B*, aided by fins attached to the upper extremity stumps, the patient uses the breast stroke in swimming. *C*, patient playing croquet. *D*, sample of patient's handwriting. *E*, patient playing table tennis. *F*, patient playing the piano. *G*, acceleration ballistocardiogram showing excellent repetition and congruity of complexes.

UNUSUAL ELECTROCARDIOGRAPHIC FINDINGS IN CARDIAC AMYLOIDOSIS

Michael Bernreiter, M.D., Kansas City, Mo.

Although amyloidosis of the heart is a comparatively rare pathological entity, one certainly should be aware of its manifestations. The diagnosis is difficult, and no specific electrocardiographic findings have been reported as far as I could learn from the study of the literature, although most observers report abnormal electrocardiograms. Common abnormalities are auricular fibrillation; low voltage of the QRS and T waves, particularly in the extremity leads; impaired auriculoventricular conduction[1]; and in the precordial leads occasionally a pattern resembling anterior wall infarction.[2] Clinically the severe form of cardiac amyloidosis leads to myocardial failure and death.[3] I have recently seen a case of amyloidosis of the heart with remarkable P-wave alternation, a phenomenon that, as far as I could determine, has not been reported in connection with the pathology under discussion. Because these findings may prove specific in cases of cardiac amyloidosis, and because I wish to stimulate others to investigate this problem, I consider this case of enough interest to report.

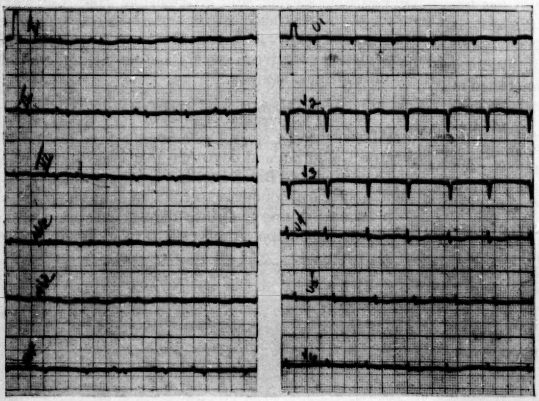

Fig. 1.—Electrocardiograms showing extremely low QRS voltage in extremity leads. Electrical alternation of P waves is best seen in lead 2.

From the Department of Electrocardiography, St. Mary's Hospital.

Report of a Case

A 52-year-old woman entered the hospital in a state of unexplained intractable heart failure with sudden onset. A liver biopsy about 10 days before death established the diagnosis of amyloidosis. An electrocardiogram was taken (fig. 1), and one is impressed with the extremely low amplitude of the QRS complexes and T waves, particularly in the extremity leads. The R waves are absent in the precordial leads V_1, V_2, and V_3, suggesting myocardial scar in the anteroseptal region. But in view of the clinical diagnosis these findings were best explained on the basis of cardiac amyloidosis. Other observers have reported that the electrocardiographic pattern of cardiac amyloidosis may be indistinguishable from that seen in myocardial infarction. The other most interesting finding is the marked P-wave alternation plainly seen in lead 2 (fig. 1, 2); as far as I could determine this has not been reported in the literature in connection with amyloidosis. This patient died rather abruptly about one week after the above electrocardiogram was taken, and the pathologist (Dr. A. Lapi) reported extensive amyloidosis of the myocardium.

Summary and Conclusions

In a case of severe cardiac amyloidosis there were unusual electrocardiographic findings. Low QRS and T-wave voltage, particularly in the extremity leads, and changes in the precordial leads suggestive of myocardial scarring have been reported by others and were present in this case. Electrical alternation of the P waves has not been reported with amyloidosis of the myocardium. It was an outstanding finding in this case and, with voltage lowering and suggestive infarct patterns, may be a helpful triad in this otherwise difficult diagnosis.

Suite 436 Professional Bldg.

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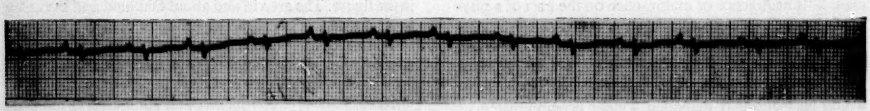


Fig. 2.—Lead 2 of same tracing shown in figure 1, with higher standard to demonstrate more clearly the electrical alternation of P wave.

The Peripheral Nerves in Old Age.—One of the most characteristic changes in an older animal is a slowing in speed of response. It has been shown in both humans and rats that reaction time becomes progressively slower in later life. . . . Such slowing of behavior is at present without explanation in terms of the structure and function of the nervous system. . . . Changes in peripheral nerve do not appear to be important in the changes in simple reaction time which occur during development and later life.—J. E. Birren and P. D. Wall, Age Changes in Conduction Velocity, Refractory Period, Number of Fibers, Connective Tissue Space and Blood Vessels in Sciatic Nerve of Rats, *The Journal of Comparative Neurology*, February, 1956.

SPECIAL ARTICLE

ANALYSIS OF PROFESSIONAL FACTORS IN MEDICAL MALPRACTICE CLAIMS

Joseph F. Sadusk Jr., M.D., Oakland, Calif.

The problem of medical malpractice claims has become increasingly severe during the past 10 years, as manifested by the rapid rise in incidence of claims, with a progressive increase in premiums for such insurance coverage. As a result, the number of carriers interested in this field of insurance coverage has steadily declined during this 10-year period. If this unfavorable trend continues, the problem may well reach the stage where the question will not be how much a physician has to pay for such insurance coverage but rather whether he can obtain coverage at any price. The general factors connected with the dissatisfaction of insurance carriers and of physicians have been outlined elsewhere.[1]

The term medical malpractice should probably be replaced by "professional liability," for physicians are not usually sued for medical malpractice but more often as an expression of the patient's dissatisfaction. Professional liability of a physician may now be looked upon as an occupational hazard.

An organized attempt to solve this complex and serious problem was initiated in Alameda County, California, in 1946. Insurance carriers had become increasingly disinterested in professional liability as individually covered through brokers, and it was apparent that some type of group coverage was necessary. The Alameda–Contra Costa Medical Association (ACCMA) set up a group program for its members, with the American Mutual Liability Insurance Company of Boston as the carrier. The following two principles (from which this program has never deviated) were laid down: 1. This was to be a coordinated program in which the insurance carrier, the legal counsel, and a carefully selected committee of the medical profession would evaluate each complaint or suit alleging malpractice on the part of a participating physician. 2. If negligence or malpractice on the part of a physician appeared to be present or if the case were indefensible, just and prompt financial remuneration would be made to the patient; however, if there were no merit to the charges brought against the physician, the doctor would be vigorously defended. Under no circumstances would a "nuisance claim" payment be made, as is so commonly done in other types of liability insurance.

Within two years, this program was so satisfactory to the physicians that it was expanded through northern and central California medical societies. About 5,000 physicians in 23 counties are now covered under this group program. Any member of a constituent county medical association may apply for coverage.

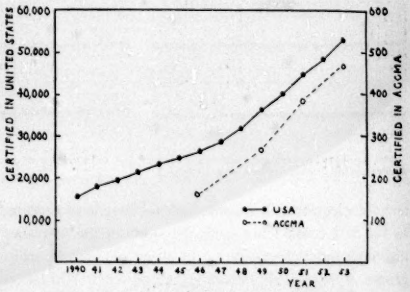
Chairman, Medical Review and Advisory Board, California Medical Association.

Read before the Alameda–Contra Costa Medical Association, April 18, 1955.

A review of the literature on medical professional liability reveals much philosophical and legal thought but few concrete facts concerning the professional factors involved. Consequently, it was considered desirable to collect accurate statistical data from the experience from 1946 through 1954 of the Alameda–Contra Costa Medical Association.[2] Appreciation should be expressed to those individuals without whose help and encouragement this study could never have been completed: the committee of physicians who reviewed the cases, our legal counsel and insurance carrier representatives who gave advice, and, finally the Alameda–Contra Costa Medical Association executive secretary and his staff who aided in the statistical analysis.

Methods and Definitions

Alameda and Contra Costa counties are located in central California and constitute that large area across the San Francisco Bay from San Francisco. The population of these two counties exceeds a million. The population increase during and since the war has been great. Physician population, as reflected by membership in our



Comparison of increase in board-certified specialists in Alameda and Contra Costa counties (California) with the United States as a whole, by total number of those certified by year.

association, was about 700 in 1946 and by 1954 had increased to 1,500. An analysis of the board-certified specialists in these two counties reveals an increase similar to that of the United States as a whole, as demonstrated in the figure. The area in and about Oakland and Berkeley in Alameda County is metropolitan in nature. Elsewhere in Alameda County the area ranges from semiurban to rural. Contra Costa County is essentially semiurban and industrial in some areas and rural in other areas.

Records of 609 complaints and suits filed in the program for the policy years 1946 through 1954 (data closed Feb. 15, 1955) were reviewed, and the facts of 125 incidents (defined below) were transferred to a coding sheet for sorting and analysis (table 1). Definitions of the terms used in this report are given below.

Suit.—A suit is the actual filing in court of a plea for recovery of damages from a physician for alleged malpractice.

Complaint.—A complaint is an accusation against a physician for an alleged act of malpractice, made in person, by telephone, or in writing by the patient or his attorney.

Ad Damnum.—*Ad damnum* refers to the amount of money asked for in the suit for damages.

Expense.—Expense includes the total cost of legal defense, court costs, expert witness expenses, and special investigation. This cost does not include insurance company overhead or salaries of company personnel.

Indemnity.—Indemnity refers to payment made to the claimant.

Judgment.—Judgment is a money award made by judge or jury after court trial.

Incident.—For the purpose of this study, incident refers to either a formal suit that has been filed or a complaint in which $100 or more was paid to settle because evidence of negligence or liability was determined by the reviewing group. These incidents were selected for statistical review below because they represent most of the cost of the program.

TABLE 1.—*Coding Sheet Used for Analysis of 125 Medical Malpractice Incidents*

MALPRACTICE PROGRAM ANALYSIS

Analysis Date.....

Dr..... Address..... Age..... Sex.....

Dr..... Address..... Age..... Sex.....

Type of Practice..... Certification..... Geog. Area.....

Type of Practice..... Certification..... Geog. Area.....

Patient..... Address..... Age..... Sex.....

Type of Injury..... Geog. Area.....

Date of Incident..... Date Complaint..... Date suit filed.....

Hospital..... Committee Review.....

Summary of Problem.....

.....

.....

.....

.....

Attorney..... Address.....

Allegation .....

.....

Closed Case: Claim..... Suit..... Amount filed.....

Settled by..... Date..... Amount paid.....

Expense.....

Total Cost.....

Open Case: Claim..... Suit..... Amount filed.....

Settled by..... Date..... Amount paid.....

Expense.....

Total Cost.....

General Statistical Review

Table 2 reveals that 94 suits were filed and 515 complaints were made during the period 1946 through 1954. Of the 94 suits filed, 2 were lost in court and judgments consequently rendered, 18 were settled since they were considered meritorious in behalf of the claimant-patient, 21 were won, 15 were dismissed by the court, and 38 are still pending. Not noted in table 2 is the fact that the total *ad damnum* filed for suits against physicians of the Alameda–Contra Costa physicians insured under the group program for 1946-1954 was $6,042,700. Still pending is an *ad damnum* of $2,893,768.

Of 515 complaints made, 436 were dismissed by the committee as totally without merit, 31 resulted in an indemnity of $100 or more being paid to the patient since the committee considered the claim with merit, and 48 are still outstanding and under review by the committee (as of Feb. 15, 1955).

TABLE 2.—*General Summary of Suits and Complaints During Period 1946-1954, Inclusive*

Suits filed		94 *
Lost	2	
Settled	18	
Won	21	
Dismissed	15	
Pending	38	
Complaints made		515
Paid indemnity	31 *	
Outstanding	48	
Dismissed	436	
Total suits and complaints		609

* 94 suits filed and 31 complaints for which an indemnity of $100 or more was paid constitute 125 "incidents."

Table 3 shows the number of physicians insured in the Alameda–Contra Costa Medical Association program for the period under study. The total number of policy years covered under this study is 8,248. The sex and age of the patients in the 125 incidents are as follows: Of the 31 complaints in this group, 8 (26%) were made by adult males, 16 (52%) by adult females, and 7 (22%) by minors (male and female combined). In the 94 suits filed, the percentage of female adults was similar (51 suits or 52%), but there was a slight increase in the number of males to 37% (35 suits) and a decrease in the case of minors to 9% (8 suits). These differences are interesting, but no satisfactory explanation can be offered.

A longer "latent period" of time occurs between the occurrence of an incident and the filing of a malpractice suit than with other types of personal liability. In 56 malpractice suits in this study, one year elapsed after the date of the incident before 77% of the suits were filed, two years before 93%, three years before 96%, four years before 97%, and more than four years before 100% of the suits were filed. The latent period of malpractice suits is undoubtedly even longer than these figures would indicate, since this study covers only nine years of total experience with a median point of approximately four years of study. Data from the New York State Group Professional Liability Program [a] indicate

TABLE 3.—*Number of Physicians Insured—Policy Years*

Yr.	No. of Physicians Insured
1946-1947	362
1947-1948	689
1948-1949	802
1949-1950	918
1950-1951	1,048
1951-1952	1,098
1952-1953	1,151
1953-1954	1,071
1954-1955	1,109
Total policy years	8,248

that up to 17 years may elapse before a given policy year for professional liability insurance coverage is dismissed. I have knowledge of one suit in California that was filed 25 years after the alleged malpractice occurred!

The long time necessary to settle or dispose of suits is demonstrated by the fact that, in the 56 malpractice suits mentioned previously, some doctors waited four years before their suits were disposed of. One year after suit was filed, only 25% of the cases were completed; two years after, 81% were completed; three years after, 94% were completed; and it was the fourth year after filing of the suit before 100% of suits were settled in this nine-year study. It is clear that the physician who is sued must undergo a long and tedious ordeal.

TABLE 4.—*Comparison of Age Distribution of Physicians by Membership and by Incidents*

Age Group	Membership, %	Incidents, %
25-29	0.4	3.2
30-34	10.0	6.4
35-39	18.1	21.6
40-44	20.5	24.8
45-49	17.0	16.8
50-54	12.0	15.2
55-59	7.6	6.4
60-64	5.3	2.4
65-69	4.1	1.6
70-74	1.9	...
75-79	1.4	1.6
80-84	0.8	...
85-89	0.4	...

Physician Age and Sex Factors

An analysis of the factor of age is made in table 4. Age groups are set up in five-year periods, and the first set of vertical data show age distribution by percentage of county membership. The vertical data to the right show age distribution in percentage of the physicians involved in the 125 incidents. It is clear that there is a slight excess of incidents in the age group from 35 to 54, while, in the age group from 55 to 69, the expected percentage of incidents is somewhat lower. This probably does not result from carelessness or inexperience of the younger physician but rather from his heavier work load as compared with that of the physician past 55 who begins to decrease his medical activity.

Comparison of sex distribution of physicians involved in the 125 incidents by membership in county societies and by incidents shows that female physicians were involved in 3.2% of incidents and that 7.8% of those who were members of county societies were female. The number of female physicians involved is approximately half that to be expected. While this appears to reflect a decreased hazard for the female physician, it should be pointed out that corrections were not possible for female physicians engaged in part-time practice, public health work, or other fields in which there is a limited exposure to malpractice claims.

Susceptibilities of Certain Physicians

An analysis of the number of incidents per physician demonstrates that 92 physicians had one incident, 10 physicians had two incidents, 3 physicians had three incidents, and one physician had four incidents. The 14 physicians who incurred from two to four incidents each constitute only 1% of the county medical association membership but account for 27% of the *ad damnum* filed, 26.6% of the *ad damnum* pending, and 24.0% of indemnity and expense paid out by the program.

Four physicians had three or four incidents each. These physicians constitute 0.3% of the county membership but account for 12.9% of the *ad damnum* filed, 17.1% of the *ad damnum* pending, and 3.5% of the indemnity and expense paid out. While the figure of 3.5% of the indemnity and expense paid out is relatively small, it is to be noted that there is a considerable number of suits pending, as expressed by the 17.1% of the *ad damnum* pending. It is likely that the percentage for indemnity and expense will increase as these suits run their course.

Type of Medical Problem

Table 5 is a breakdown of the 125 incidents by the type of medical problem. Whether the analysis is made by percentage of incidents, by percentage of *ad damnum* filed, or by percentage of indemnity and expense paid out, surgical cases account for the great majority. The table shows that 85 of the 125 incidents, or 68%, were surgical in nature. Medical problems follow next with the relatively small percentage of 18.4%, radiological problems account for 2.4%, and equipment problems (such as diathermy burns, hot water bottle burns, electrosurgical [Bovie] burns, and heat lamp burns) account for 5.6%. Other miscellaneous problems account for the remaining 56%.

Twenty-three medical incidents accounted for 18.4% of cases. An analysis of these 23 medical incidents reveals that internal medicine problems (principally toxic drug reactions) accounted for 13 incidents, or 48.6% of *ad damnum* filed and 52.6% of the indemnity and expense. Neuropsychiatric problems of varying types accounted for seven incidents, 45.7% of *ad damnum* filed, and 39.5% of the indemnity and expense. Pediatric problems accounted for three incidents, 5.7% of *ad damnum* filed, and 7.9% of the indemnity and expense. Other medical fields such as dermatology and allergy were not represented.

TABLE 5.—*Distribution of Incidents by Type of Medical Problem*

	Incidents		*Ad Damnum* Filed, %	Indemnity and Expense, %
	No.	%		
Medical	23	18.4	22.3	18.3
Surgical	85	68.0	69.6	71.9
Radiological	3	2.4	1.3	1.3
Equipment	7	5.6	1.8	7.4
Other	7	5.6	5.0	1.1
Total	125	100.0	100.0	100.0

Surgical incidents are analyzed and summarized in table 6. Obstetrics and gynecology, orthopedics, and general surgery lead the list and account for 61 of the 85 surgical incidents. The remaining subspecialties of surgery played a much less important role. The emergence of obstetrics and gynecology as the numerically leading field was unexpected. Orthopedics has long been considered the major professional liability hazard, however, and retains its lead in the amount of indemnity and expense paid out.

Geographical Area of Practice

It is interesting to compare geographical areas of practice, since rural areas have been considered to be a lesser hazard than urban areas. While it was not possible, because of the small numbers involved in this study, to compare the truly rural areas with truly metropolitan areas of the counties, an analysis was made by counties.

Alameda County constitutes the majority of membership (87%), since it includes Oakland and Berkeley, two large metropolitan areas. This county accounted for 81.6% of the 125 incidents, 76.3% of *ad damnum* filed, and 85.1% of the indemnity and expense. Contra Costa County (13% of membership), in contrast, consists of a rural and semiurban area and consequently should reflect significantly for an analysis between the metropolitan versus the semiurban and rural areas. It accounted for 17.6% of incidents, 19.6% of *ad damnum* filed, and 14.9% of the indemnity and expense. (Other areas accounted for 0.8% of incidents and 4.1% of *ad damnum* filed.) Regardless of how one analyzes the problem, by number of incidents, by *ad damnum* filed, or by indemnity and expense paid out, there is no significant difference between the two counties.

TABLE 6.—*Distribution of Eighty-Five Surgical Incidents*

	No.	*Ad Damnum* Filed, %	Indemnity and Expense, %
Obstetrics-gynecology	25	29.1	25.8
Orthopedics	18	15.5	35.3
General	18	24.8	18.3
ENT	5	1.3	1.2
Plastic	4	4.4	8.9
Neurosurgery	4	13.3	1.7
Ophthalmology	4	5.8	0.9
Thoracic	3	0.9	4.5
Anesthesia	2	3.7	1.7
Proctology	1	1.2	0.6
Urology	1	....	1.1
	85	100	100

Type of Practice of Physician

Many theories have been advanced concerning the relative hazard of physicians according to the type of practice they perform. Some have considered the general practitioner a greater hazard than the specialist. While this study was not large enough to permit the division of physicians into types of specialty practices, it was possible to make certain broad divisions between the general practitioner and the specialist and to divide each of these main groups into two smaller groups.

A comparison between all general practitioners and all specialists in the 125 incidents studied shows that general practitioners accounted for 44.4% of members, 54.4% of incidents, 47.8% of *ad damnum* filed, and 48.7% of the indemnity and expense. It is clear that there is no valid difference in liability of the general practitioner versus the specialist. Indeed, if one further breaks down these two broad groups into two groups each, namely, dividing specialists into those who are certified by one of the American boards and those who are not certified by a board and dividing the general practitioners into those who are members of the American Academy of General Practice and those who are not, again no significant difference is demonstrated (table 7). Consequently, it is clear that the type of practice that a physician performs is not significant in his being a hazard in the professional liability field. The board-certified specialist is apparently just as much of a hazard as the general practitioner. Whether the general practitioner is a member of the American Academy of General Practice likewise makes no difference.

TABLE 7.—*Breakdown of General Practitioners into Members and Nonmembers of AAGP and of Specialists into Certified and Noncertified Specialists* *

	Membership, %	Incidents, %	*Ad Damnum* Filed, %	Indemnity and Expense, %
Non-AAGP members	27.0	32.8	31.4	27.2
AAGP members	17.0	21.6	16.4	21.5
Noncertified specialists	24.0	15.2	15.6	26.7
Certified specialists	31.4	30.4	36.5	24.6
Total	100.0	100.0	100.0	100.0

* AAGP stands for American Academy of General Practice and certified specialist indicates certification by the American specialty boards.

The Hospital

It has always been assumed that the professional liability hazard is greater in the hospital than in office or home practice, since more difficult and complicated procedures, leading to an irreducible number of complications, are carried out in the hospital. An analysis of location of the 125 incidents in this study proves this assumption. Approximately 70% of the incidents occurred in the hospital, while only 30% occurred in the physician's office or in the patient's home. Incidents in hospital accounted for 75% of the *ad damnum* filed and 77% of the indemnity and expenses paid.

If one further breaks down this difference in hazard by the type of practice that the physician performs, such incidents appear to increase in the hospital with increasing specialization. Table 8 indicates that the specialist has a higher percentage of incidents occurring in the hospital. This difference is possibly explained by the fact that the specialist handles the more complicated surgical problem in contrast to the general practitioner who generally confines himself to the less complicated type of surgery. Again the fact that complicated and dangerous surgery will result in an irreducible number of complications seems clear.

TABLE 8.—*Distribution of 125 Incidents Occurring in or out of Hospital by Type of Practice of Physician*

	% of Incidents	
	In Hospital	Out of Hospital
General practice	52	48
General practice (AAGP)	73	27
Specialists	90	10
Certified specialists	70	30
All general practice	60	40
All specialists	79	21

Finally, it is interesting to analyze the degree of hazard among the various hospitals. Table 9 shows malpractice incidents among the 17 hospitals in Alameda and Contra Costa counties per 100,000 admissions to each hospital and the cost to the physicians' malpractice program per

hospital admission. This does not include hospital liability. All county, governmental, and closed-panel group hospitals are excluded, since such physicians have not generally been included in our group program.

It will be noted that the number of malpractice incidents per 100,000 admissions ranges from zero in the case of hospital no. 14 (a small, new hospital that possibly does not have sufficient experience), to a high of 56.4 incidents per 100,000 admissions in hospital no. 11. The cost to the physicians' malpractice program in that hospital was $2.33 per patient admitted. The median rate for all hospitals was 12 per 100,000 admissions. These differences among the hospitals are remarkable and probably the most interesting fact obtained in our analysis.

TABLE 9.—*Distribution of Malpractice Incidents Among Hospitals, by Number of Incidents per 100,000 Admissions and Cost to the Program per Each Hospital Admission* *

Hospital, No.	Rate/100,000 Admissions	Cost/ Admission of Indemnity and Expense
1	2.2	$ .03
2	12.5	.07
3	6.1	.06
4	4.6	.06
5	15.0	.48
6	33.0	1.10
7	12.3	.14
8	4.8	.10
9	13.3	.17
10	19.8	.43
11	56.4	2.33
12	9.8	.14
13	7.0	.03
14	...	....
15	14.0	.14
16	11.6	.50
17	15.9	.27
Median	12.0	.14

* All county, governmental, and closed-panel group hospitals are excluded in this table.

Comment

The data presented in the present study are based on a relatively small number of physicians and policy years as well as a relatively small number of claims and suits. Also, the period of study is brief, with only nine years of total experience and with the median point of study of approximately four years. Studies with larger programs of longer duration may bring out more accurate statistics, and such statistics may give importance to other factors. However, I hope that this study will encourage other investigations into this field, so that much needed facts about professional liability may be learned.

This limited study shows that the following factors do not appear important in professional liability: (1) age of physician, (2) sex of physician, (3) geographical area of practice, and (4) general practice versus specialty practice. Important factors in medical malpractice appear to be (1) the type of medical problem involved, (2) the hospital, and (3) multiple incidents of certain physicians, who appear to be "malpractice prone."

With regard to the type of medical case, it is clear that all surgery is of importance, with obstetrics and gynecology, orthopedics, and general surgery leading. The emergence of obstetrics and gynecology as the leading problem is noted for the first time in an appraisal of this subject.

The second point of importance is that of the hospital in itself, since there was found an unusually wide spread of malpractice incidence among the hospitals for the acts of physicians. It is clear that each hospital must survey its staff problems in the light of professional liability and regulate the practice of physicians who are responsible for an untoward number of malpractice claims.

Finally, it is clear that the malpractice-prone physician is a hazard to any group professional liability program. Prevention programs must be directed at such physicians for their education both medically and legally. It is doubtful that they can be educated through general meetings or through informative literature.

There are many other factors in malpractice claims, but it is not yet possible to obtain accurate and specific data on them. The unwise and unkind comments or criticisms of physicians with regard to treatment given by another physician, the patient's attempt to cancel a physician's fee by malpractice threats, and the failure of the physician to point out the potential hazards of a diagnostic or surgical procedure or to point out the inability of guaranteeing results are other causes of malpractice losses.

Still other causes are the increasing tendency of the public to seek financial remuneration for real or imaginary damage; the increasing tendency of juries to award more frequent and higher judgments; and inflation, necessitating higher payments for claims, judgments, and defense. The unfavorable articles in lay magazines dealing with costs of medical care, fee splitting, and medical malpractice bring antagonism against the physician, while the favorable articles on new drugs, methods of treatment, and modern miracle surgery lead the public to believe that a less than perfect result must be evidence of negligence.

In the meantime, as Ford [4] pointed out years ago, prevention of medical malpractice depends upon three points: (1) good faith, (2) good records, and (3) common sense. Good faith implies that the physician treat his patient with tact and kindness, that he conceal no known difficulty in diagnosis or treatment, and that he advise consultation freely. Good records require that the physician adequately document his medical records of the patient, carefully record untoward happenings, and make a matter of record the treatment given and advice offered. Common sense implies that the physician know the vindictiveness of some patients, recognize the hazard connected with the collection of reluctant fees, be aware of the failure of equipment that in turn can produce injury, and, finally, use only well-established medications and procedures.

Summary

An analysis of the professional factors in a group liability program of 8,248 policy years over a period of nine years in two adjacent counties of central California reveals the important factors to be (1) the type of medical problem involved (surgical versus medical), in which obstetrics and gynecology, orthopedics, and general surgery lead the field; (2) the individual hospital; and (3) multiple claims against certain physicians. The nonim-

portant factors are (1) age of physician, (2) sex of physician, (3) geographical area of practice, and (4) general practice versus specialty practice.

459 30th St. (9).

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DIAGNOSTIC PROBLEMS

PRESENTATION OF CASE

Earl P. Benditt, M.D., Chicago

A 40-year-old woman was admitted to Billings Hospital from the emergency room on July 3, 1954. Her chief complaint on admission was dyspnea of three weeks' duration. About one month prior to admission, she first noted upper abdominal pain that was rather sharp and that was accentuated by coughing or hiccuping. This pain became progressively worse. About two weeks prior to admission, she noted slight exertional dyspnea and, because of this, was hospitalized elsewhere. At that hospital electrocardiograms, gastric analyses, and roentgenograms of the chest, gallbladder, and gastrointestinal tract, all of which were normal according to the patient, were obtained. Her liver at that time was large and somewhat tender. Her dyspnea grew worse daily. She was told that this was probably caused by anxiety and that she should not consider it of any importance and was discharged. When she came to the emergency room, her dyspnea had progressed to the point where it was distressing, even on a regimen of strict bed rest. In the 10 days prior to admission, she noted the onset of a cough productive of 1 or 2 teaspoonfuls of sputum per day, occasionally rust-colored and some times black. There was no history of gastrointestinal disease, and she had not been jaundiced. In June of 1953, a left radical mastectomy had been performed for a lump in the left breast that had been diagnosed as carcinoma. No recurrence of this had been noted in the intervening year. The patient had been a heavy drinker prior to February, 1953. She had been under psychiatric care for four years, but this care had been intermittent.

Physical Examination.—On admission the patient was dyspneic and agitated. Her blood pressure was 140/70 mm. Hg, pulse 104 per minute, respirations 36 per minute, and temperature 39 C (102.2 F). There were numerous hemangiomas (nevus araneus) over her trunk and several ecchymotic areas on both anterior superior iliac crests. A hard mass, 1 cm. in diameter, was palpated in the subcutaneous tissues over the left anterior superior iliac spine. No lymph nodes were palpable. There was a well-healed left mastectomy scar, with no evidence of recurrent tumor. Her right breast was normal. Her chest was clear to percussion. A few scattered rales and inspiratory squeaks were heard throughout both lungs. Her heart was normal, except that the pulmonic second sound was louder than the aortic second sound. Her liver was palpated at the level of the umbilicus and was irregularly nodular, firm, and nontender.

Laboratory Findings.—The results of the Kahn and Eagle tests were reported as being doubtful; the leukocyte count was 7,300 per cubic millimeter, hemoglobin level 13 gm. per 100 ml., erythrocyte count 3,900,000 per cubic millimeter, hematocrit 36%, and sedimentation rate 31 corrected to 21. The differential count was normal. The urine on admission showed a trace of albumin; bile was present on the "shake" test; and microscopic examination revealed occasional hyaline and granular casts, many leukocytes, and occasional epithelial cells. The urea nitrogen level was 35 mg. per 100 ml.; total protein level, 5.8 gm. per 100 ml. (albumin 3.0 and globulin 2.8); cholesterol level, 140 mg. per 100 ml., with 85 mg. per 100 ml. of cholesterol esters; and bilirubin level, 2.2 mg. per 100 ml., direct, and 3.4 mg. per 100 ml., indirect. Cephalin flocculation was 3 +; thymol flocculation, 4 +; and alkaline phosphatase, 9.7 Bodansky units per 100 ml.

Course.—On the day after admission the patient's dyspnea was not improved by any therapy tried. A roentgenogram of the chest was entirely normal. Because of this and the absence of pulmonary findings, the patient's psychiatrist was consulted. He believed that her dyspnea was most probably not on a hysterical basis. On this same day she became slightly cyanosed and, because of this, she was given 100% oxygen, which relieved the cyanosis. Despite this, she remained dyspneic. Although there was no history to suggest it, it was believed that she might have some abnormality in oxygen transportation, and the hemoglobin was studied to see whether any methemoglobin was present. None was found. The patient's condition remained essentially the same until the fourth hospital day, when she was found to be in shock. An electrocardiogram revealed a right bundle-branch block. Numerous cultures that had been taken during the hospitalization were negative. An unsuccessful attempt was made to start treatment with levarterenol, but the patient died.

Anatomic Diagnosis

At autopsy no recurrence of tumor was evident in the left breast region. Mild fibrocystic disease was present in the right breast. The liver was enlarged, weighed 3 kg., and, in addition to passive hyperemia and fatty change, contained many tumor metastases. Enlarged lymph nodes were present in the porta hepatis and peripancreatic region. These were infiltrated largely by a moderately well differentiated adenocarcinoma having some well-formed glandular tissue with no mucus and abundant tumor giant cells. The structure of the tumor was compatible with that of a ductal-type adenocarcinoma of the breast. The spleen weighed 550 gm. and showed numerous metastases in the red pulp and at the margins

From the Department of Pathology, University of Chicago.

of residual follicles. The most striking metastatic phenomenon was seen in the lungs. Here numerous small pulmonary artery radicles contained tumor emboli (see figure). Most of these were fresh. A few older, partly organized emboli were also present, indicative of previous smaller embolic showers. The lumbar vertebral bone marrow showed tumor metastases and a striking erythroid hyperplasia. The heart weighed 400 gm. and showed dilation and mild hypertrophy of the right ventricle.

Section of lung showing tumor emboli filling branches of pulmonary vessel.

COMMENT

Robert G. Page, M.D.
and
Fausto Tanzi, M.D., Chicago

This case presents an infrequently recognized sequence of events: carcinomatous embolization of the lungs from breast cancer metastatic in the liver. A similar case was described by Mason in 1940.[1] There is, however, an interesting difference between his patient and the one here presented. His patient, like those of Greenspan [2] and Brill and Robertson,[3] who also had metastatic cancer to the smaller pulmonary vessels, died of failure of the right side of the heart. This patient had no clinical evidence of failure of the right side of the heart, but died of anoxia. Fulton [4] describes these two types of death and states that the anoxic death occurs in the more rapidly progressive disease. This patient had symptoms of three weeks' duration. The anatomic evidence is compatible with the occurrence of several showers of tumor emboli. The earlier showers produced dyspnea and cyanosis and the final shower, sufficient anoxia to kill. The constellation of dyspnea, a "normal" roentgenogram of the chest, and a previous history of cancer was at first thought to be caused by anxiety. It seems more reasonable to consider the symptoms under such circumstances to emanate from organic disease.

From the Department of Medicine, University of Chicago.

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COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following report has been prepared at the request of the Council on Foods and Nutrition. The Council would appreciate being notified of any increased incidence of infantile scurvy in other localities.

EUGENE H. STEVENSON, M.S.
Acting Secretary.

INFANTILE SCURVY

THE INCREASING INCIDENCE OF SCURVY IN THE NASHVILLE AREA

Calvin Woodruff, M.D., Nashville, Tenn.

Scurvy continues to occur among the infant population in the United States despite advances in the knowledge and application of the principles of nutrition. This is illustrated by the experience in the wards and clinics of Vanderbilt University Hospital during the last 28 years. Throughout this period staff members of the pediatric service have been actively interested in scurvy and in ascorbic acid metabolism; therefore, it seems unlikely that the increased incidence results from changes in recognition of the disease or the accumulation of cases referred for special study. Inquiries among the pediatricians and the general practitioners in the Nashville area have confirmed our impression of a real increase in the incidence of infantile scurvy. Simultaneously, there has been a decrease in the incidence of other deficiency diseases in the adult population of this hospital during the past decade, and deprivational rickets has become a rarity in the pediatric service.

All of the 103 cases in which infantile scurvy was diagnosed at Vanderbilt University Hospital from 1926 through 1954 have been reviewed. Only those cases in which the diagnosis was made from clinical or radiological evidence were included. As no essential change was apparent in the clinical picture during this period,

From the Department of Pediatrics and Division of Nutrition, Vanderbilt University School of Medicine.

an analysis of the material provides a clinical description of the disease. The incidence of scurvy is presented in table 1. It might appear that the peaks in the incidence are related to World War II and the Korean action, but actually the trend of increasing frequency appears to be unaffected by these times of unrest. It is noteworthy that

TABLE 1.—*Incidence of Infantile Scurvy at Vanderbilt University Hospital*

Period	Pediatric Out-patients, Total Visits	Scurvy Cases	Incidence/ 1,000 Visits
1926-1934	83,887	8	0.10
1935-1939	65,786	11	0.17
1940-1944	55,435	15	0.27
1945-1949	44,381	24	0.59
1950-1954	48,084	45	0.94

scurvy occurred infrequently during the depression years, when a large part of our population was suffering from severe economic stress and when pellagra and protein deficiency were relatively common.

The age of the infants on admission to the hospital is presented in table 2. The great majority of the cases occurred in infants between the ages of 7 and 11 months. The occurrence of scurvy in infants under 5 months of

TABLE 2.—*Scurvy Patients Admitted to the Hospital*

Age, Mo.	No.	Age, Mo.	No.
5	1	12	6
6	6	13	3
7	22	14	5
8	11	15	3
9	15	16-18	1
10	11	19-24	5
11	11	Over 24	3

age is rare, and only one case of congenital scurvy has been reported in the United States.[1] The infant is well supplied with ascorbic acid at birth; this supply is adequate to protect him from scurvy for about 5 months. The appearance of scurvy in an infant after the age of 15 months is also unusual. Reasons for the presence of scurvy in these older infants will be discussed in connection with the feeding history. The virtual absence of scurvy in infants over 2 years of age is attributable to

TABLE 3.—*Onset of Symptoms in Scurvy Patients*

Month	No.	Season	Total No.
January	9	Winter	31
February	10		
March	12		
April	8	Spring	24
May	7		
June	9		
July	9	Summer	20
August	8		
September	3		
October	12	Fall	28
November	7		
December	9		

their more varied diet even under the poorest conditions of feeding.[2] Not included in this series is one case of scurvy occurring in a 14-year-old deaf child who was living in an institution. Such exceptional cases resemble scurvy in adults both in manifestations and in pathogenesis.

In the past, scurvy found in adults has been associated with periods of prolonged confinement and dietary restriction caused by long sea voyages, crop failures, wars, and the like.[3] In all these circumstances, the lack of fresh foods was the determining factor in the development of the deficiency. In more recent studies of infantile scurvy, the availability and price of oranges has been an important seasonal factor.[4] The months of onset of the symptoms in the present series is found in table 3. Al-

TABLE 4.—*Chief Complaint on Admission of Infants with Scurvy*

	No.
Tenderness of the legs	39
Pseudoparalysis	28
Irritability	13
Red or bleeding gums	7
Swelling over the long bones	2
Nonspecific history	2
Unilateral exophthalmos	1
Bloody diarrhea	1
Fever	1
No complaints referable to scurvy	9
Total	103

TABLE 5.—*Duration of Symptoms in Infants with Scurvy*

	No. of Cases
Diagnosis on admission	9
Less than 1 wk.	20
1 wk. to 1 mo.	46
2 mo.	19
Over 2 mo.	8
Unknown	1
Total	103

TABLE 6.—*Frequency of All Symptoms Recorded in Scurvy Patients*

	No. of Cases
Tenderness of legs	78
Irritability	71
Pseudoparalysis of legs	65
Anorexia	32
Hemorrhagic gums	21
Diarrhea	20
Fever	19
Tenderness of arms	14
Swelling over long bones	14
Pseudoparalysis of arms	12
Tenderness after trauma	10
No specific symptoms	9
Cessation of sitting	6
Cessation of standing	6
Weight loss	6
Melena	5
Hemorrhagic skin changes	4
Discoloration of eyelids	3
Tenderness of chest wall	3
Epistaxis	2
Hematuria	1

though there is a slight increase in the number of cases occurring in the early fall and late winter, the seasonal incidence with a peak in September previously noted is conspicuously absent. In other words, variations in the supply of antiscorbutic foods attributable to seasonal fluctuations are not important factors in the incidence of scurvy at the present time. Similar findings have been reported by McIntosh.[5] Also, neither sex nor race appears to play a determining role in the occurrence of scurvy.

Presenting Symptoms

The chief complaints listed in the records of the scorbutic infants are enumerated in table 4; the duration of these symptoms is presented in table 5; and in table 6 are listed all the symptoms recorded in the order of their frequency. It is apparent that there was no single symptom common to all of the patients. On the other hand, the frequency of the triad of irritability, tenderness of the legs, and pseudoparalysis (failure to move or use the legs) was characteristic in the majority of the histories obtained. Involvement of the arms in pseudoparalysis was less common. In 10 infants the parents attributed the tenderness and pseudoparalysis to minor trauma such as tripping on the bed clothes. Failure to use the extremities was also expressed as cessation of sitting or standing. In three infants soreness of the chest with respiratory difficulty reflected painful involvement of the costochondral junctions.

Fig. 1.—The "pithed frog" position in a scorbutic infant who also has a hemorrhagic rash in the diaper area and ecchymosis of both eyelids. The fullness in the right thigh suggests the presence of a subperiosteal hemorrhage.

A history of bleeding or its manifestation was the presenting symptom in 11 instances. In 21 of the infants hemorrhage around erupting teeth or frank bleeding from the gums was noted. Bleeding from all of the body orifices except the vagina was noted at least once. The infrequency of hemorrhagic skin manifestations in these histories is in contrast to the picture of scurvy in the adult. The most common nonspecific symptoms listed were anorexia, diarrhea, and fever.

Physical Findings

A typical patient with infantile scurvy lies quietly in his crib and cries when approached, as if in anticipation of a painful experience. The "pithed frog" position as depicted in figure 1 was assumed by half of our patients. This is a position of comfort with the legs flexed at the knees and the hips both partially flexed and externally rotated. Costochondral beading (fig. 2) was found by palpation in 80 patients and was the most frequent physical finding (table 7). Because this sign is also present in rickets and has been one of the reasons for much confusion between these two diseases in the past, attempts have been made to differentiate the types of beading seen in these two diseases. The typical changes seen in scurvy consist of subluxation of the cartilaginous portion of the anterior chest wall on the bony lateral portion, producing an abrupt or sharp transition. This has been referred to as a bayonet deformity because of its similarity to the sharp drop felt by the passage of the finger past the end of the barrel of an Army rifle with a fixed bayonet. The beading in rickets is more rounded. Although sharp beading was more frequently found in our study, the presence of a significant number of instances of rounded deformity in the absence of rickets suggests that this is not a reliable means of differentiating between these diseases.

TABLE 7.—*Frequency of Physical Findings in Scurvy Patients*

	No. of Cases	
Costochondral beading		80
"Sharp"	69	
"Rounded"	11	
Tenderness		67
Generalized	39	
Right leg	11	
Left leg	12	
Arms	5	
"Pithed frog" position		52
Hemorrhagic gums		44
Temperature over 100 F (37.7 C)		44
Palpable subperiosteal hemorrhages		48
Around knee	29	
Ankle and wrist	19	
Hemorrhagic skin lesions		12
Discoloration of eyelids		5
Exophthalmos		1
Atypical costal retraction		3
No specific findings		1

Fig. 2.—Costochondral beading in a scorbutic infant. The prominence of the costochondral junctions can be seen extending downward from the nipple.

Tenderness was listed as a physical finding if the infant showed signs of distress when handled. In most cases the tenderness was generalized; when localized in the legs, both legs were involved to the same extent. Tenderness on movement of the arms was less common and usu-

ally was present in addition to involvement of the lower extremities. Hemorrhage around erupting teeth was consistently present (fig. 3). In the younger infants a crown of turgid, red, redundant gum was seen about the central incisors. In older infants the erupting first molar was similarly involved. In advanced scurvy the gums

Fig. 3.—Hemorrhage into the gums around the upper central and lateral incisors, particularly on the right, is typical of the usual gum lesions.

bled after minimal manipulation. In those infants in whom teeth had not yet erupted and in edentulous areas, the gums were invariably found to be normal in appearance.

Palpable subperiosteal hemorrhages were found in 48 patients. Their greater frequency in the distal end of the femur and proximal end of the tibia is in accord with the predominance of radiological changes in these areas. Only 12 patients had hemorrhagic manifestations in the skin. In contrast to the characteristic perifolliculitis of scurvy occurring in adults, petechial eruptions are relatively uncommon in infantile scurvy. The early symptoms and signs of scurvy found in adults differ from those occurring in infantile scurvy. One infant had retrobulbar hemorrhage with protrusion of one eye and discoloration of the lid as the chief complaint (fig. 4). Similar periocular manifestations occurred in four other patients. In two the lesions were bilateral and consisted of hemorrhage into the soft tissue around the eye without exophthalmos. Temperature higher than 100 F (37.7 C) occurred in about half of the patients. It was often present even though no infection could be found, but it disappeared during treatment. Although fever is a frequent finding in cases of uncomplicated scurvy, its presence does not necessarily indicate that there is presence of infection.

Roentgenographic Findings

Radiographs of the long bones were made in all but seven patients in this series. Changes characteristic of scurvy, which are described later, were present in 88 patients. In six patients changes in the bones of an indeterminate nature were found, and in two no lesions could be demonstrated on the films. Since the clinical picture in these eight patients was clear-cut, it is probable that the lesions in the bones had not developed to the extent that they could be recognized. One case, with a diagnosis of scurvy made on the basis of the radiological findings alone, showed severe growth failure; in one other the disease was diagnosed by means of the roentgenologic picture before the disease was suspected clinically.

The characteristic changes in the radiographic appearance of the long bones in infantile scurvy are at the cartilage-shaft junction. They appear earliest at the sites of most active bone growth such as the sternal ends of the ribs, the distal end of the femur, the proximal end of the humerus, both ends of the tibia and fibula, and the distal ends of the radius and ulna. The knees may show diagnostic findings even when only minimal changes are present at the wrist. Several specific signs are present in scurvy, but no one alone is diagnostic; they may all exist in other diseases. Cortical atrophy or diminution of the ratio between the thickness of the cortex and the thickness of the shaft is an early alteration. The cortex normally is thinned to a mere hairline close to the cartilage-shaft junction; this thin cortex may be completely absent in scurvy (fig. 5*A*). Atrophy of the trabecular structure with increased transparency and blurring or loss of the trabecular markings occurs, giving rise to a "ground glass" appearance. Widening of the zone of provisional calcification casts a dense shadow at the end of the shaft. A similar change occurs at the periphery of the centers of ossification best seen about the knee (fig. 5*B*). When accompanied by rarefaction and loss of trabecular markings in the epiphyseal center, this change is almost specific for scurvy and it aids in making the differential diagnosis.

Fig. 4.—Infant having a retrobulbar hemorrhage with unilateral exophthalmos as well as extensive ecchymosis of the left eyelid.

A zone of rarefaction immediately shaftward of the zone of provisional calcification corresponds to an area of histological disorganization and dissolution, the "scorbutic lattice." At first this zone of rarefaction is apparent only near the cortex and, in conjunction with the extreme thinning of the cortex or its virtual disappearance on the roentgenogram, constitutes the "corner sign" or "corner fracture" described by Park.[4] This is one

of the earliest useful diagnostic findings. As the scorbutic process proceeds, this area of rarefaction may extend across the whole width of the cartilage-shaft junction. This area is weak and the trauma of normal movement and weight bearing may produce fractures. The overlying zone of provisional calcification may be comminuted into the shaft, obliterating the area of rarefaction. When this occurs the wider zone of provisional calcification will extend beyond the cortex, producing spur formation. Separation of the epiphysis may also occur at this area with lateral displacement. In the larger bones this may occur with comminution and obliteration on one side and separation and widening at the other. These changes are the most conspicuous ones seen in this disease.

Fig. 5.—*A*, roentgenographic appearance of the wrist in moderately severe scurvy, illustrating the thickened zone of provisional calcification. The area of decreased density proximal to the zone of provisional calcification is easily recognized near the cortex—a typical "corner fracture" with virtual disappearance of the cortex at the margin of the bone. *B*, x-ray showing condition present in knees of same patient. The uniform ground glass appearance of the bones and the ring-like appearance of the distal femoral and proximal tibial epiphyses are characteristic of scurvy. *C*, after two weeks of treatment, the extensive subperiosteal hemorrhages of the femurs, which were not apparent radiologically in *B*, have calcified. New bone growth at the distal end of the femur is already apparent.

The thickened, brittle zone of provisional calcification also fractures easily under the stress of normal activity. The center may be comminuted into the shaft and the edges mushroomed outward, giving rise to spur formation. Early calcification of the separated periosteum where it is attached to the cartilage may form a spur of a similar type. Calcification along the rest of the periosteum occurs only during the healing process and is the result of ossification. The radiological picture may be modified by some degree of temporary healing. The size of subperiosteal hemorrhages is often less than suspected from the increase in size of the soft tissue shadows. This distortion is caused by edema and hemorrhage outside the periosteum. After several days of treatment, bone formation by the periosteum will clearly outline the area of hemorrhage (fig. 5*C*). As healing continues, the density of the bone increases, growth in length is resumed, and normal architecture is gradually restored. Even the grossest deformities secondary to subperiosteal hemorrhage or subepiphyseal separation will resolve without other than antiscorbutic therapy, although radiological evidence of their presence may persist for several years.[6]

Hematology

In almost one-half of the patients in this series, the hemoglobin level was below 10 gm. per 100 ml. of blood. The hypochromic anemia of iron deficiency was the most common anemia. Megaloblastic anemia of infancy was diagnosed in three instances by means of bone marrow aspiration. Ten cases of anemia could not be classified because of insufficient information in the records. In some of these patients there was significant infection.

The majority of the leukocyte counts made when the patients were first seen ranged from 4,000 to 20,000 per cubic millimeter. Leukocytosis with an increase of 10,000 cells per cubic millimeter or more was present in half of the patients. Two patients had leukopenia with megaloblastic anemia. Almost all seven patients with cell counts over 20,000 per cubic millimeter had localized bacterial infection.

Concomitant Disease

The distribution of diseases found in these scorbutic patients is similar to any general hospital experience. It is not characteristic of scurvy but does reflect the susceptibility to infection of scorbutic infants. It is most interesting that a diagnosis of rickets was made only six times. The concomitant occurrence of rickets and scurvy has not been seen by me since 1947.

Pathology

The principal morphological effects of ascorbic acid deficiency are found in the mesenchymal tissues.[7] There is a failure of deposition of intercellular substances by the fibroblasts, osteoblasts, and odontoblasts, leading to defective collagen, osteoid, and dentine. There is also a general failure in the deposition of intercellular cement substances manifested principally by rupture of the capillaries. In infants the defect in collagen formation in the soft tissues is reflected principally by bleeding into the gums subsequent to the trauma of tooth eruption. Bleeding into the skin is probably caused by minor trauma or by increased venous pressure. The occasional bleeding from the kidneys, intestine, and nose represents fragility or spontaneous rupture of capillaries. The absence of bleeding into the central nervous system in this series and the relative infrequency in other reported cases are fortunate. Enlargement of the heart and tachycardia may occur and are probably caused by involvement of the connective tissue of the cardiac muscle. Sudden death in scorbutic infants has been attributed to these cardiac changes.[8]

The major manifestations of infantile scurvy are found in the growing bones. The role of ascorbic acid in bone growth has been extensively studied in the guinea pig[9] and in infants.[2] All of the morphological changes in scorbutic bones are caused by lack of osteoid formation. The zone of provisional calcification becomes thickened

because it is not replaced by normal bone. The area immediately shaftward from the zone of provisional calcification is unresistant to the stresses and strains of motion and weight bearing because dissolution of bone continues to occur. Histologically, spicules of calcified matrix are found in considerable disarray beneath the cartilage. Pinkish-staining hyaline material, large numbers of red blood cells, quantities of apparently impotent osteoblasts, and macrophages containing hemosiderin are found around the fractures. As scurvy in the human is rarely absolute, some degree of healing is apparent with osteoid and bone surrounding some of the fractures.

The deposition of osteoid ceases throughout the shaft of the long bones; however, destruction of the trabeculae in the marrow cavity and the dense cortical bone continues at a normal rate. The cortex is thinned and the trabeculae diminish in size. The periosteum loses its firm attachment to the shaft of the bone, and hemorrhages result from microscopic fractures at the cartilage-shaft junction and easily dissect their way along the shaft. Since the attachment of the periosteum to the cartilaginous epiphysis remains intact, these hemorrhages do not extend beyond the zone of the provisional calcification. Changes in the teeth have been regularly observed in experimental scurvy in guinea pigs. Failure to find changes in dentine formation in infantile scurvy is probably explained by the slow rate of growth of the teeth of infants.

Metabolic Functions

The pathological findings in scurvy are principally due to the role of ascorbic acid in maintaining the normal function of intercellular substances. Other biochemical defects can be demonstrated in scorbutic infants. The amino acid tyrosine is not completely metabolized when it is fed in relatively large amounts, but this defect is easily corrected by administration of ascorbic acid.[10] Numerous other metabolic aberrations have been found in experimental animals.[11]

Dietary Histories

Scurvy occurs in infants only after relatively prolonged ingestion of a diet devoid of, or grossly deficient in, ascorbic acid. An analysis of the dietary histories in our series of patients illustrates both the types of diets that are associated with the development of scurvy and some of the reasons why antiscorbutic foods were not included in the regimen in adequate amounts (table 8).

All of the infants in this series had been artificially fed for at least three months before the onset of scorbutic symptoms. Ninety-eight of the patients had received artificial feeding consisting of evaporated milk or pasteurized whole milk, and five had received a proprietary formula. Thirteen infants had been breast fed for over six weeks; in nine of these scurvy developed between 3 and 10 months after cessation of nursing, with an average interval of 6⅓ months. Two infants received small amounts of antiscorbutic irregularly, and the onset of scurvy was delayed. One severely retarded infant ate no solid foods, and scurvy developed when the child was 3 years old, two years after nursing was discontinued. Thus, scurvy will develop in infants three or more months after cessation of nursing if no antiscorbutic is administered.

The 11 histories of adequate intake of orange juice (3 oz. or more per day) were too perfect to be believed. In one of these cases, prevarication was admitted by the parents after it became obvious that their child was well again. The frequency with which such spurious histories were obtained may reflect feelings of guilt by the parents as they begin to realize the source of their child's suffering. In two cases in which the antiscorbutic was discontinued, the orange juice was stopped on the advice of a physician, evidently without effective recommendation of another source of ascorbic acid.

Diagnosis

The diagnosis of scurvy depends upon a history of negligible ascorbic acid intake, the presence of symptoms suggestive of the disease, typical physical findings, and specific radiological changes. It is apparent from our experience that all four of these points may not be present in every case. In 11 cases a presumably spurious

TABLE 8.—*History of Intake of Ascorbic Acid in Infants with Scurvy*

		No. of Cases
Insufficient		85
Orange juice irregularly	18	
Small amounts of vegetables	6	
Indefinite history	4	
Reduced by vomiting	3	
Heating orange juice	1	
Wet ascorbic acid tablets	1	
Tomato juice irregularly	1	
Orange-flavored drink	1	
Antiscorbutic not offered		81
Despite medical advice	3	
"Doing so well without any"	1	
Reason not specified	27	
Antiscorbutic refused by infant		11
Antiscorbutic discontinued		8
Reason unknown	3	
Sore mouth	2	
Rash	2	
Diarrhea	1	
Proprietary preparations not containing ascorbic acid		7
Adequate		11
Total		103

dietary history was given. In nine cases the diagnosis was made on admission on the basis of physical findings alone. In one case the diagnosis rests on radiological changes only. In many instances the initial diagnosis was made in the outpatient department on the basis of typical history and physical findings without dependence on the x-ray picture. The combination of tenderness and pseudoparalysis of the lower extremities, beading of the ribs, and hemorrhages around the erupting teeth is sufficiently characteristic of scurvy to establish the diagnosis, especially in combination with a history of deficient ascorbic acid intake. In patients with less clear-cut findings, roentgenologic examination will often be helpful.

Differential Diagnosis

The differential diagnosis of scurvy usually presents no problems if the physician is familiar with the disease and considers it in his diagnosis. Some of the mistakes in diagnosing scurvy in my experience will illustrate the problems that arise. Recently an effort was made by the

admitting officers to record for one year the final diagnosis on all patients referred with symptoms suggesting poliomyelitis. Seven of the 23 patients who later were found to have diseases other than poliomyelitis had scurvy.[12] These 7 accounted for one-half of the cases of scurvy that were seen during that particular year. Confusion arising from failure to recognize the pseudoparalysis of scurvy is probably responsible for the majority of the mistakes in diagnosis made when patients

TABLE 9.—*Fasting Serum Ascorbic Acid Concentration in Sixty-Three Patients with Scurvy*

Mg./100 Ml.	No.	%
Less than 0.10	56	89
0.10 to 0.19	2	3
0.20 to 0.29	2	3
More than 0.29	3	5
Total	63	100

are first seen. Several of our patients were initially sent to the State Crippled Children's Clinic with clinical diagnoses varying from congenital dislocation of the hip to dyschondroplasia. One patient was treated with a hip spica cast for one week before it was realized that he had scurvy. The presence of fever and elevated white blood cell count is probably responsible for the frequent initial impression of infection. One infant who had chest pain due to costochondral fractures was considered to have pleurisy. Confusion with rickets was common because of the wider experience with this disease in the past by many of the referring physicians. One patient with a hemorrhagic, seborrheic rash was given a diagnosis of Letterer-Siwe disease until help was obtained from x-ray findings. On initial examination, cases with unilateral exophthalmos may be hard to differentiate from those of tumors of the eye. The limited age range in which scurvy usually occurs is perhaps the most helpful point in suggesting the possibility of this disease. X-rays of the long bones of infants with pseudoparalysis, swellings in the long bones, or hemorrhagic phenomena not readily explained on another basis should assist in clarifying the diagnosis.

Clinical Biochemistry

Laboratory assessment of ascorbic acid nutriture is not universally available. We have had the opportunity of measuring the ascorbic acid concentration in the serum of 63 patients with scurvy. Experimental studies of scurvy in the human would suggest that ascorbic acid is absent from the serum for many weeks before the appearance of the disease (table 9).[13] The method used is not sensitive to concentrations of less than 0.10 mg. of ascorbic acid per 100 ml. of serum. Eighty-nine per cent of the patients could be considered as having no detectable ascorbic acid in their serum. The remaining 11% had significant fasting serum levels at a time when they were determined clinically to have scurvy. Several of these patients had received variable amounts of orange juice between the time when they were first seen by a physician and the time that they reached the hospital. Occasionally it was suspected that the routine administration of orange juice in the ward in the early morning was not omitted as had been requested. The presence of ascorbic acid in the serum is not compatible with a biochemical diagnosis of scurvy. It is quite possible that these patients were tested at a time when the clinical and radiological picture was still present although the biochemical lesion was at least partially corrected. Since most of them were treated subsequently, it is impossible to know which ones would have shown healing without further treatment.

Ascorbic acid concentrations of 0.0 mg. per 100 ml. of serum were frequently found in subjects who did not have scurvy, but such values do not establish a diagnosis. Accordingly we have employed the saturation test of Kajdi, Light, and Kajdi [14] to differentiate between the scorbutic patient and the patient who has a fasting level of 0.0 mg. due to lack of recent intake and essentially normal body stores. In table 10 it may be noted that 48% of the scorbutic subjects had no ascorbic acid in the serum four hours after the intramuscular injection of 200 mg. of ascorbic acid. An additional 44% had concentrations between 0.10 and 0.39 mg. per 100 ml. Since one of the patients with a four-hour concentration of 0.39 mg. per 100 ml. was unable to metabolize adequately an added load of tyrosine, it seemed certain that this degree of saturation was compatible with the development of scurvy. The remaining 8% in all likelihood had received some recent treatment in amounts inadequate to produce a clinical remission.

Treatment

The response of a child with scurvy to treatment with ascorbic acid is dramatic. There is a remarkable change from irritability and peevishness to a pleasant disposition and from anorexia to a thriving appetite. The infant is usually symptom-free within three or four days. Cessation of hemorrhagic phenomena occurs early, and hemorrhages around erupting teeth will bleach almost overnight. The amounts of ascorbic acid required to obtain this response are surprisingly small. Dramatic responses to single doses of 4 oz. of orange juice have been reported in the past.[3] Present-day treatment with large doses of synthetic ascorbic acid given orally has not produced any more rapid clinical results although saturation of the tissues may be achieved more rapidly by this means. The advantage of small divided doses over larger single daily doses is difficult to evaluate. Healing of the

TABLE 10.—*Serum Ascorbic Acid Concentrations* *

Mg./100 Ml.	No.	%
Less than 0.10	12	48
0.10 to 0.19	4	16
0.20 to 0.29	3	12
0.30 to 0.39	4	16
More than 0.39	2	8
Total	25	100

* Four hours after intramuscular administration of 200 mg. of ascorbic acid in patients with fasting levels below 0.10 mg. per 100 ml.

skeletal lesions is noticeable within one week with calcification of subperiosteal hemorrhages, but the reparative processes necessary to correct the bony deformities may take several years. As the tissues become saturated with ascorbic acid, the serum concentration level becomes elevated. Repeated determination of a saturation test shows this most clearly (fig. 6). Although relatively small doses will produce a clinical response, treatment should be designed to restore to normal the depleted

stores of this vitamin. In the author's opinion this can be accomplished by doses of 200 mg. given orally every day for a week or 10 days.

Requirement

The minimal requirement of ascorbic acid in infants is not established with exactness. It has long been appreciated that the regular administration of one tablespoonful of orange juice daily, which supplies about 8 mg. of ascorbic acid, will prevent the development of a clinically evident case of scurvy.[3] Even smaller doses might be equally effective for this purpose. Since the normal newborn infant has stores of ascorbic acid adequate to prevent development of scurvy for some five months, and since breast feeding results in the accumulation of stores of similar magnitude, the provision of amounts of ascorbic acid equivalent to those in breast milk would appear to ensure the continual presence of adequate stores of ascorbic acid. The recommended dietary allowance of the Food and Nutrition Board of the National Research Council (table 11) provides intakes roughly equivalent to those of the breast-fed infant.

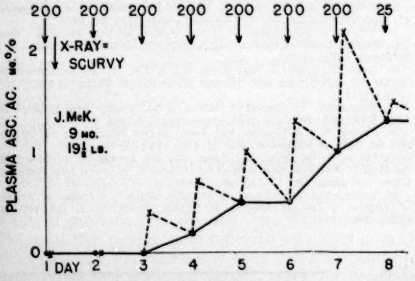

Fig. 6.—Fasting plasma ascorbic acid levels (solid line) and those found three hours after parenteral administration of 200 mg. of ascorbic acid. (Adapted from Mindlin, R. L.: *J. Pediat.* **17**: 621, 1940.)

Prevention

Scurvy can be prevented only by the provision of adequate supplies of ascorbic acid in the diets of infants. Orange juice is a food well suited to this purpose and in 2-oz. daily doses beginning during the first month of life will provide the recommended daily allowance of ascorbic acid. For those infants who persistently refuse orange juice or for those few in whom symptoms develop with its administration, the substitution of other antiscorbutic foods (table 12) or synthetic ascorbic acid should be instituted.

Several proprietary formulas for infants have been fortified with ascorbic acid during the last decade. Although this move has prevented the further occurrence of scurvy in infants fed these formulas without further supplementation, the philosophy of adding to the milk all of the nutrients required by infants may be carried too far. Since the most important attribute of a normal, complete diet for children is a variety of foods, it is the responsibility of all those who care for infants to assist in developing wide taste acceptance and to begin this education early in life. The importance of an antiscorbutic in the diet is a first lesson. Consequently it is unfortunate to have the point of this lesson lost in the maze of fortified formulas and multivitamin preparations with which we are confronted every day.

Pathogenesis

Scurvy occurs in individuals who ingest foods devoid of ascorbic acid for periods of about five months. Are there factors other than dietary deficiency, such as increased requirements during illness or rapid growth, that account for the restricted age distribution summarized in table 2? A complete answer to this question is not possible because knowledge of the exact ascorbic acid requirement at different ages in childhood is not available. If rapid growth were an important factor, one would expect to find a higher incidence in premature infants. On the other hand it is reasonable to suspect that premature infants receive more thorough medical care, including ascorbic acid administration.

TABLE 11.—*Recommended Dietary Allowances of Ascorbic Acid* *

Age, Yr.	Mg. Males	Females
1-3 mo.	..	30 ..
4-9 mo.	..	30 ..
10-12 mo.	..	30 ..
1-3	..	35 ..
4-6	..	50 ..
7-9	..	60 ..
10-12	75	.. 75
13-15	90	.. 80
16-20	100	.. 80
21-45	75	.. 70
45-65	75	.. 70
65	75	.. 70
Pregnancy	..	.. 100
Lactation	..	.. 150

* National Research Council Publication 302, revised 1953.

Greater difficulty comes in explaining the disappearance of scurvy after the age of about 15 months. The analysis of cases presented previously demonstrates several situations in which diets devoid of ascorbic acid will produce scurvy in older infants. The studies of Follis are particularly pertinent at this point because the pathological diagnosis is much more sensitive than a clinical diagnosis.[2] The age distribution of Follis's cases is similar to most of the published series.[15] Since small amounts of ascorbic acid are known to prevent scurvy in this age group, it does not seem possible that an increased requirement exists at this age period. The premature infant fed a high-protein diet may be an exception to this conclusion.[16]

TABLE 12.—*Common Foods Supplying Thirty Milligrams of Ascorbic Acid*

Food	Amount, Oz.
Orange juice, fresh	2
Orange juice, canned	2½
Grapefruit juice, fresh	2½
Grapefruit juice, canned	3
Tomato juice, canned	6½

Consequently one must examine the factors associated with diets devoid of ascorbic acid that apply to the age group of infantile scurvy and ask if they are sufficient to account for the increasing incidence in this disease at the present time. In our own experience, seasonal factors associated with the availability of the antiscorbutic foods do not appear to play a significant role in this problem. Synthetic ascorbic acid in various vitamin preparations

or as ascorbic acid tablets is widely available. Orange juice in the canned or frozen state is just as available to our patients as is the evaporated milk that they drink. One of the factors that has played a role in the past is the destruction of ascorbic acid in fresh milk by heating. Pasteurization of milk followed by reheating in the preparation of a formula will destroy most of the ascorbic acid originally present; however, boiling fresh milk for 5 minutes does not destroy its antiscorbutic property. The number of infants in this area fed fresh milk from the family cow has greatly decreased during the last 30 years. The concept of "complete" infant formulas has been rather widely accepted. A number of cases of scurvy were observed before the addition of ascorbic acid to replace that which was destroyed during processing. The advantages to health coincident with the pasteurization and sterilization of the milk supply and its fortification with vitamin D far outweigh the loss of its antiscorbutic properties. Furthermore, these changes in the milk supply have been present for many years and do not coincide in time with the increase in scurvy in our hospital.

In 1939 a survey of ascorbic acid levels in the serum of children attending this clinic was made.[17] Thirty-six per cent of the "normal" children and 62.5% of the "sick" children under 3 years of age had serum ascorbic acid concentrations below 0.3 mg. per 100 ml. The low incidence of scurvy found clinically or radiologically in this group was commented upon at that time. Concentrations of ascorbic acid in the serum that were "satisfactory" (above 0.7 mg. per 100 ml.) occurred in children whose diets did not contain any orange or tomato juice but did contain "pot liquor." "Pot liquor" is the water in which green vegetables and fat meat have been boiled, often for moderately prolonged periods, and its administration has been a time-honored practice in nonscientific infant feeding in the South. An analysis of "pot liquor" from turnip greens revealed an ascorbic acid content of 16 to 28 mg. per 100 gm. despite the loss of about one-half of the ascorbic acid content of the leaves themselves.[18] The value of this substance as an antiscorbutic is apparent. At the present time "pot liquor" is not widely used. This valuable custom has been discarded without adequate realization of its antiscorbutic role, while, for economic reasons or through ignorance, carelessness, or neglect, the scientifically recommended prescribed feeding regimen is only partially adopted.

This bit of local folklore is but an example of the effect of the refinement of infant foods on nutrition. Both sterilization of the formula and abandonment of old customs in infant feeding have reduced the ascorbic acid intake of infants and have made supplementation by either citrus juices or vitamin preparations mandatory. At the same time the importance of these supplementary practices has not been adequately realized. Consequently there has been an increase in the incidence of scurvy in those families either lacking adequate medical supervision or failing to appreciate its value.

Summary

The incidence of infantile scurvy at Vanderbilt University Hospital has increased during the years 1926 through 1954. This increasing incidence is attributed to failure to ensure an adequate intake of ascorbic acid rather than unavailability of good food or medicinal sources of this vitamin. Increasing urbanization, together with the abandonment of time-honored practices in infant feeding in this area, has been proposed as a possible etiological factor.

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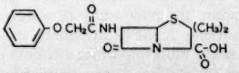
COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

Monographs and supplemental statements on drugs that appear in this column have been authorized by the Council for publication and inclusion in New and Nonofficial Remedies. They are based upon the evaluation of available scientific data and reports of investigations.

H. D. KAUTZ, M.D., *Secretary*.

Phenoxymethyl Penicillin.—Penicillin V.—An antibiotic produced by fermentation that contains a phenoxymethyl group instead of the benzyl group present in penicillin G.—The structural formula of phenoxymethyl penicillin may be represented as follows:



Actions and Uses.—Phenoxymethyl penicillin exhibits an antibacterial spectrum similar to that of soluble salts of penicillin G. (See the general statement on penicillin in New and Nonofficial Remedies.) Phenoxy-

methyl penicillin is more resistant to inactivation by gastric juices than other oral penicillin preparations and therefore is better absorbed from the gastrointestinal tract. As a result, blood levels are obtained that are higher than when a like amount of the salts of penicillin G is administered by mouth. The absorption of the drug does not appear to be diminished if administered after meals. Current evidence suggests that most of the common pathogens amenable to penicillin therapy are as sensitive to phenoxymethyl penicillin as to penicillin G. In general, the therapeutic range of effectiveness of orally administered phenoxymethyl penicillin appears to be similar to that of penicillin G given orally. Unless administered in larger doses, however, phenoxymethyl penicillin is not as effective as parenterally administered aqueous preparations of penicillin G. For this reason, parenteral administration of penicillin G remains the treatment of choice in severe, acute infections caused by organisms susceptible to penicillin therapy.

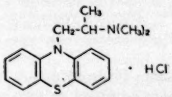
Phenoxymethyl penicillin is effective in the treatment of infections caused by hemolytic streptococci, pneumococci, gonococci, and susceptible micrococci (staphylococci). It is well tolerated by mouth but, in common with all orally administered antibiotics, can cause occasional diarrhea. Like other penicillin preparations, phenoxymethyl penicillin can elicit symptoms of sensitivity ranging in severity from mild erythema and hives to frank serum sickness. To date, such symptoms have been infrequent. In rare instances its administration may also cause acute anaphylactic shock, although this is less likely than after parenteral administration of other penicillin preparations; however, it should be used with caution in patients with bronchial asthma, allergy, or a history of previous penicillin reaction. Current evidence suggests that patients with urticarial sensitivity to penicillin G may not necessarily show cross sensitivity to phenoxymethyl penicillin; in such cases, the physician should proceed with caution.

Dosage.—Phenoxymethyl penicillin is administered orally. The usual dose for the treatment of moderately severe infections caused by hemolytic streptococci and susceptible micrococci is 125 mg. (200,000 units) three or four times daily. In subacute bacterial endocarditis or severe infections when bacteremia is present, a parenteral aqueous preparation of penicillin G should be employed. For the treatment of pneumonias, the initial dose of phenoxymethyl penicillin is 250 to 300 mg. (400,000 to 500,000 units) followed by 125 mg. (200,000 units) every 4 hours. To prevent recurrent attacks of rheumatic fever, 125 to 300 mg. (200,000 to 500,000 units) may be administered daily. As a prophylactic against secondary infection after minor surgical procedures in patients with rheumatic fever or heart disease, the usual dose is 125 mg. (200,000 units) every 8 hours. In acute gonorrheal infections, 125 mg. (200,000 units) every 4 hours for five or six doses has proved effective. In such cases, laboratory studies are indicated to rule out the possibility of concomitant syphilis.

Preparations for use as stated for the foregoing drug are marketed under the following names: Pen-Vee-Oral; V-Cillin.

Eli Lilly & Company and Wyeth Laboratories, Inc., cooperated by furnishing scientific data to aid in the evaluation of phenoxymethyl penicillin.

Promethazine Hydrochloride, N. F. — 10-(2-Dimethylaminopropyl)phenothiazine hydrochloride.—The structural formula of promethazine hydrochloride may be represented as follows:



Actions and Uses.—Promethazine hydrochloride, one of the phenothiazine group of compounds, exerts a histamine-antagonizing action of somewhat longer duration than that of most other drugs of this pharmacological class. It is useful for the treatment of all types of allergic conditions amenable to therapy with antihistamines. These include urticarial dermatoses, pruritic lesions, allergic rhinitis, and drug reactions. Like other antihistamines, its usefulness in asthma is decidedly limited. (See the general statement on histamine-antagonizing agents in New and Nonofficial Remedies.)

Promethazine hydrochloride has been found useful for the treatment of both airsickness and seasickness. Its clinical usefulness in the treatment of vertigo caused by other vestibular disturbances has not been evaluated. It has been used to control postoperative nausea and vomiting.

Like other antihistamines, promethazine hydrochloride depresses the central nervous system, its activity in this respect being somewhat more pronounced than that of many of the other histamine-antagonizing agents. Although the drug may produce drowsiness in many patients, it is not to be regarded as primarily a sedative. Other side-effects occasionally observed with other antihistamines may occur. To date, there have been no reports of jaundice, hypotensive episodes, or blood dyscrasias associated with the use of this agent.

Dosage.—Promethazine may be administered orally, intramuscularly, or intravenously. For allergic conditions amenable to therapy with antihistamines, the average oral dose is 25 mg., taken before retiring, followed by 6.25 or 12.5 mg. the next day, as required to control symptoms. As an alternative, 12.5 mg. after meals and on retiring may also be administered.

For the treatment or prophylaxis of motion sickness, the average oral dose for adults is 25 mg. two or three times daily. The initial dose should be taken 30 to 60 minutes before boarding ship or plane and may be repeated 8 to 12 hours later if necessary. On succeeding days of travel, 25 mg. may be taken on arising and before the evening meal.

For those patients suffering from acute allergic disorders in whom the oral route is not feasible, a dose of 12.5 to 25 mg. for adults may be administered intravenously or intramuscularly. This may be repeated within 2 hours if necessary, but oral therapy should be substituted as soon as possible. To minimize postoperative nausea and vomiting, intramuscular doses of 25 mg. one-half hour before surgery and repeated at intervals of 1 to 4 hours as necessary have been used. Dosage for children by all routes of administration is reduced proportionately. Because of associated drowsiness, prometha-

zine hydrochloride, like most antihistaminics, should not be administered to persons operating vehicles or machines requiring constant alertness.

Preparations for use as stated for the foregoing drug are marketed under the following name: Phenergan Hydrochloride.

Wyeth Laboratories, Inc. cooperated by furnishing scientific data to aid in the evaluation of promethazine hydrochloride.

Corticotropin–Zinc Hydroxide.—A preparation of purified corticotropin adsorbed on zinc hydroxide.

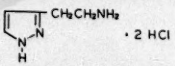
Actions and Uses. — Corticotropin–zinc hydroxide elicits the same metabolic effects and is used for the same indications as other corticotropin preparations. Because of its combination with zinc hydroxide, however, absorption after parenteral administration is apparently delayed. Its action is thus prolonged, and therapy may be maintained with less frequent administration, with similar precautions and similar dangers. (See the monograph on corticotropin in New and Nonofficial Remedies.) The duration of action in those patients whose conditions require high dosage, for example, those with acute disseminated lupus erythematosus and acute asthma, appears to be shorter than in those requiring lower dosage, for example, those with rheumatoid arthritis.

Dosage.—The potency of corticotropin–zinc hydroxide is expressed in terms of activity equivalent to a specified number of U. S. P. units of corticotropin. It is administered intramuscularly and should not be mixed with other medicaments before administration. As with other corticotropin preparations, dosage must be individualized for each patient according to the severity of symptoms and therapeutic response. The usual initial dose is 40 U. S. P. units injected once daily intramuscularly as a suspension. Once symptoms have been controlled, the interval between injections should be increased and the dosage reduced.

Preparations for use as stated for the foregoing drug are marketed under the following name: Cortrophin-Zinc.

Organon, Inc., cooperated by furnishing scientific data to aid in the evaluation of corticotropin–zinc hydroxide.

Betazole Hydrochloride.—3-(β-Aminoethyl) pyrazole dihydrochloride.—The structural formula of betazole hydrochloride may be represented as follows:



Action and Uses.—Betazole hydrochloride, an analogue of histamine, can be used in place of histamine in clinical tests of gastric secretion. The drug effectively stimulates the secretion of hydrochloric acid with much less tendency to the side-effects usually observed after the use of histamine. In addition, betazole produces no significant fall in blood pressure and only minimal increases in pulse rate.

In usual doses, betazole hydrochloride produces a gastric secretory response that is at least as great as that produced by the usual doses of histamine. During the first hour after a single injection, the response is quantitatively similar, but evidence suggests that a greater output of free acid is maintained after a lapse of 2 hours or more. The drug occasionally stimulates gastric secretion in patients who do not respond to histamine.

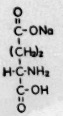
Although the incidence of side-effects with betazole is much lower than with histamine, the nature of these is qualitatively similar. Flushing, sweating, and a sense of warmth are observed in about 20% of patients receiving the drug. Headache occurs in about 3% of such patients. Rarely, urticaria, faintness, and syncope follow the use of this agent. The drug should be used cautiously in patients with bronchial asthma. The effect of antihistaminic drugs in combating the side-effects has not been determined.

Dosage.—Betazole hydrochloride may be administered by intramuscular or subcutaneous injection; the latter route is usually employed. In general, a dose of 0.5 mg. per kilogram of body weight will evoke the same gastric secretory response as the usual dose of 0.01 mg. of histamine base per kilogram or 0.0275 mg. of histamine phosphate per kilogram. Because of its wide margin of safety, most clinicians usually administer a standard dose of 50 mg. of betazole hydrochloride to all patients of normal weight. If this does not produce the desired response in large individuals, an increased amount may be administered.

Preparations for use as stated for the foregoing drug are marketed under the following name: Histalog.

Eli Lilly & Company cooperated by furnishing scientific data to aid in the evaluation of betazole hydrochloride.

Sodium Glutamate. — Monosodium-L-glutamate. — The structural formula of sodium glutamate may be represented as follows:



Actions and Uses.—Sodium glutamate, the monosodium salt of L-glutamic acid, is used for the symptomatic treatment of encephalopathies associated with diseases of the liver. Although the biochemical nature of the metabolic disturbance is complex and imperfectly known, some cases have been found to be associated with elevated blood ammonia levels. In the central nervous system, excessive ammonia is associated with symptoms of lethargy, confusion, and ultimately coma and convulsions. The role of sodium glutamate in alleviating these symptoms is thought to be related to promotion of glutamine synthesis from glutamate and ammonia. This detoxication mechanism is known to function in vitro in brain slices from experimental animals. Whether this reaction occurs in vivo in the central nervous system of man is not known. In both man and animals, however, the administration of glutamic acid or its salts is followed by a fall in the blood ammonia level.

Sodium glutamate has been found useful in clearing mental symptoms and lowering blood ammonia levels in a small number of comatose patients with liver diseases associated with ammoniacal azotemia. There is no evidence that the drug has any effect on the ultimate course of the disease. Its symptomatic effectiveness has been most pronounced in patients in whom mental symptoms have been precipitated by circulatory nitrogenous loads of exogenous origin. These include administration

of ammonium chloride or protein hydrolysates, internal hemorrhage, or high-protein diet.

Evidence is lacking that the glutamate ion per se produces any serious toxic effects in man. Administration of the sodium salt, however, represents a serious potential danger that is associated with the cation sodium. Since sodium glutamate is metabolized to yield, in effect, equivalent amounts of sodium, its metabolic effects are similar to those produced by the administration of equimolar quantities of sodium bicarbonate. In the dosage employed in the therapy of hepatic encephalopathies, these effects may result in a serious and even life-endangering alkalosis and hypokalemia. It is therefore important for the physician using this salt to observe closely the acid-base status of the patient and to determine the blood carbon dioxide, chloride, sodium, and potassium levels at frequent intervals. The intravenous administration of large amounts of sodium might also be quite dangerous to a patient with cirrhosis of the liver and attendant fluid retention. Sodium glutamate is contraindicated in patients with anuria, oliguria, or signs of renal insufficiency.

The limited clinical experience with sodium glutamate appears to confirm the good theoretical basis for its administration; however, since the drug has been employed in only a relatively small number of cases, the demonstration of even its temporary benefit has necessarily been limited to a small number of patients. Its use is not indicated in patients with hepatic disease that is not associated with elevated blood ammonia levels and when the danger of severe electrolyte disturbance is great. Although oral administration of the drug would seem preferable to intravenous administration, dosage by the oral route has not been sufficiently studied to permit a definite declaration of the average dose. In addition, the gravity of hepatic encephalopathies frequently precludes oral therapy.

Dosage.—Sodium glutamate is administered intravenously. The initial average dose for adults per 24 hours is 29 gm. For administration, a solution containing 29 gm. of sodium glutamate in 100 cc. of water is diluted with 1,000 cc. of 5 or 10% dextrose in water for injection. The diluted solution, containing 170 mEq. of sodium, is then slowly infused by intravenous drip over a period of 4 hours. In some cases, it may be necessary to infuse additional amounts of the drug; however, this should be done cautiously, and no more than 58 gm. of the sodium salt should be administered in any 24-hour period.

Preparations for use as stated for the foregoing drug are marketed under the following name: Glutavene.

Gray Pharmaceutical Company cooperated by furnishing scientific data to aid in the evaluation of sodium glutamate.

Additional Uses of Methylbenzethonium Chloride

The Council has evaluated additional uses of methylbenzethonium chloride, a quaternary ammonium compound, for rinsing undergarments and bed linen of incontinent adults and for topical application in the prevention and treatment of dermatitis caused by irritation from urine, feces, and perspiration. The Council previously has recognized the use of this nonvolatile, antibacterial agent for making a 1:25,000 diaper rinse in the prevention of ammonia dermatitis (diaper rash) in infants. On the basis of currently available evidence, the Council concluded that the use of this compound for rinsing diapers or garments and for topical application is justified in the prophylaxis as well as in the treatment of dermatitis caused by the bacterial break-down of ammonia in the urine of infants and incontinent adults. Sufficient evidence is also available to warrant its use for treatment of miliaria (prickly heat) and erythema intertrigo (chafing) caused by perspiration and stool contamination. For topical application, an ointment containing 1 mg. per gram or a 0.055% dusting powder may be applied ad libitum to the skin of the genitalia, rectum, thighs, and intertriginous areas.

The Council also was requested to evaluate the usefulness of methylbenzethonium chloride as a rinse to impart wide antibacterial properties to autoclaved surgical garments and laundered hospital linens for reducing the incidence of surgical wound infection and odors. A review of the evidence indicated need for continued investigation to establish the usefulness of the agent for these purposes.

The Council voted to expand the monograph in New and Nonofficial Remedies to recognize the additional use of methylbenzethonium chloride for rinsing garments of incontinent adults and for topical application to infants and adults in the prevention and treatment of dermatitis caused by contact with urine, feces, and perspiration.

The Diaparene Company, Division of Homemaker's Products Corporation cooperated by furnishing scientific data to aid in the evaluation of additional uses of methylbenzethonium chloride.

CHEMICAL LABORATORY

TESTS AND STANDARDS FOR NEW AND NONOFFICIAL REMEDIES

The last edition of Tests and Standards that contained all monographs for nonofficial products that appeared in New and Nonofficial Remedies was published in 1953. There is now available a supplement to this 1953 edition. The present supplement contains Tests and Standards monographs on nonofficial products accepted by the Council on Pharmacy and Chemistry, under its former seal-acceptance program, between Jan. 1, 1953, and Jan. 1, 1955. This includes all new products, all new dosage forms of previously accepted products, nonofficial dosage forms of official products that were Council-accepted, and any monographs extensively revised since 1953. This completes the Tests and Standards that were prepared under the now discontinued acceptance program.

The 161-page supplement is bound in a pliable paper cover and contains 105 monographs. The supplement can be obtained from the Order Department of the American Medical Association, 535 N. Dearborn St., Chicago 10, Ill. The purchase price is $2.

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THE NEW N. N. R.

The 1956 edition of New and Nonofficial Remedies, just off the press of the J. B. Lippincott Company, reflects an important change in the scope of information that is to be included in this well-known annual publication of the A. M. A. Council on Pharmacy and Chemistry. The new edition implements for the first time in book form the revised program for evaluation of drugs that the Council instituted during 1955 to render a better service to the medical profession.[1] Under its revised method of operation, the Council issues monograph statements on all individually available new drugs on the basis of currently available evidence, whether or not such information is adequate at the time to determine their ultimate importance or usefulness in medicine. Wherever possible, attempts also are made to compare or show the relationship of new drugs to older and well-established drugs. Accordingly the N. N. R. section of the Council's column of THE JOURNAL and the book, both of which formerly were restricted to descriptions of relatively well-established drugs, now provide more complete coverage of current information on drug therapy. The N. N. R. section of the Council's column of THE JOURNAL also has been made more newsworthy to physicians by publication of supplemental statements concerning evaluated new uses, routes of administration, or significant changes in the therapeutic status of previously evaluated drugs. This added feature of the N. N. R. section of THE JOURNAL replaces the former procedure of listing commercial dosage forms and sizes. New and Nonofficial Remedies, in both column and book form, thus has become a more complete source of clinical information on individual drugs and excludes technical information respecting pharmaceutical dosage forms or sizes. The time saved by the elimination of product information amply provided by pharmaceutical concerns has made it possible for the Council to evaluate the evidence for many more drugs than was possible under its former procedure. The 1956 edition of N. N. R. contains 58 new monographs on drugs not described in the previous edition.

New and Nonofficial Remedies continues to describe drugs under suitable nonproprietary terminology and to include both proprietary and nonproprietary names for the various commercial preparations of individual drugs concerning which the Council is informed.[2] Names of commercial preparations (exclusive of dosage form terminology) are listed as a matter of information in conjunction with monographs and in the index of the book without the name of the manufacturer or distributor. The listing of such names no longer is restricted to those complying with the principles used in selecting nonproprietary (generic) names, so that physicians who may be unfamiliar with this terminology can more readily identify preparations by one or more of the names under which they are marketed. Future editions of N. N. R. will include additional names as the Council is informed of their applicability to preparations for use of individual drugs as described in the publication.

Evaluation of ready-prepared mixtures of drugs for monograph description in N. N. R. has been discontinued to enable the Council to concentrate its primary effort on the evaluation of available evidence pertaining to the actions, uses, dosage, hazards, and other pertinent properties of individual drugs. Publication of timely information on each new compound should make it easier for the physician to judge which combinations are best suited for the individual patient on the basis of the Council's evaluation of separately available component drugs.

Physicians and other users of New and Nonofficial Remedies should realize that this publication has ceased to function as a book that describes only selected or well-established drugs. By publishing monograph statements for inclusion in N. N. R. concerning any and all new drugs (exclusive of mixtures) at the earliest opportunity, the Council seeks to provide more comprehensive and up-to-date information on the basis of which physicians may exercise their own clinical judgment in the selection of therapy for patients. The Council believes that this approach to the dissemination of unbiased information on new drugs will better enable both physicians and medical students to keep abreast of developments in the rapidly expanding field of therapeutics.

1. New Program of Operation for Evaluation of Drugs, statement of the Council on Pharmacy and Chemistry, J. A. M. A. **158**: 1170-1171 (July 30) 1955.
2. Listing of Trade Names, statement of the Council on Pharmacy and Chemistry, J. A. M. A. **160**: 50 (Jan. 7) 1956.

SEROTONIN

Recent reports that carcinoid tumors may be rich in serotonin (5-hydroxytryptamine) and that certain antagonists of serotonin evoke unusual mental changes have stimulated interest in the pharmacological and physiological actions of this interesting compound, a normal constituent of the body.

The isolation and identification of serotonin from body tissues was effected independently by two groups of workers. Erspamer [1] and his associates were interested in isolating the substance responsible for the histochemical properties of the enterochromaffin cells of the gastrointestinal tract. They named this substance enteramine and in 1952 identified it as 5-hydroxytryptamine. Meanwhile, Page [2] and his associates had succeeded in isolating and identifying as 5-hydroxytryptamine a substance from blood serum long known to possess vasoconstrictive properties. This substance had previously been known by a variety of names, including serotonin and vasotonin.

Subsequently, serotonin was shown to be present in the brain, the highest concentrations being found in areas associated with the autonomic system and in the area postrema.[3]

Serotonin is apparently elaborated by the cells of the enterochromaffin system, the precursor being tryptophan. In the blood stream, serotonin is closely associated with the platelets, which may act as carriers for this agent, protecting it from amine oxidase, by which free serotonin is rapidly destroyed. The source of serotonin in the brain has not been established. The main metabolite of serotonin in human beings, dogs, and rats is 5-hydroxyindoleacetic acid.

In vitro and in vivo experiments indicate that the actions of serotonin include stimulation of smooth muscle of blood vessels, of the gastrointestinal tract, of the bronchi, and of the estrual uterus. The in vitro effects can be readily antagonized by a number of naturally occurring compounds, including the ergot alkaloids, the harmala alkaloids, and yohimbine, all of which bear some structional relationship to serotonin. Woolley and Shaw [4] have suggested that the antagonistic effect of these compounds can be explained by competitive inhibition and have prepared a number of synthetic analogs antagonistic to serotonin. Most of these antimetabolites have at most only a very weak action against the circulatory effects of serotonin in the intact animal.

In 1954, Thorson and his associates [5] drew attention to a variety of bizarre clinical findings, including valvular lesions of the right side of the heart, peripheral vasomotor symptoms, diarrhea, asthma, and cyanosis, seen in association with certain cases of malignant carcinoid. Similar cases were promptly reported by a number of other investigators, and evidence is now available to support the suggestion of Thorson and his group that many, if not all, of the bizarre effects may be due to the elaboration of excessive amounts of serotonin by the tumor cells. Thus serotonin has been isolated from such tumors.[6] Furthermore, patients with this syndrome have high titers of serotonin in the blood and high concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the urine.[7] It has also been reported that withholding tryptophan from such a patient resulted in a fall in urinary 5-hydroxyindoleacetic acid.[8] While certain effects, such as the vascular phenomena, the diarrhea, and the asthma, may well be directly related to high titers of serotonin in these patients, Sjoerdsma and Udenfriend suggested that other effects, such as a pellagra-like condition of the skin and possibly the heart lesions, may be due to niacin deficiency caused by the bulk of the dietary tryptophan being diverted into serotonin formation. Preliminary attempts to alleviate the symptoms with known serotonin antagonists have as yet proved unsuccessful, a finding consistent with the difficulty of demonstrating any action of such drugs against the pressor effects of serotonin in the intact animal.

The suggestion that serotonin may play an integral role in the functioning of the nervous system is an intriguing one. The fact that certain serotonin antagonists such as lysergic acid diethylamide evoke a schizophrenia-like reaction led Woolley and Shaw to suggest that the presence of serotonin is necessary for the maintenance of normal mental processes and that certain mental illnesses may be the result of serotonin deficiency. Alternately, it was conceded that the serotonin antagonists might retard the destruction of the serotonin and that the mental aberrations evoked by such compounds could be due to the accumulation of excessive amounts of serotonin. Pletscher, Shore, and Brodie [9] favor the former viewpoint. These investigators observed certain similarities between the central effects of serotonin and of reserpine. They further found that urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid is increased after administration of reserpine to dogs and that serotonin is liberated from the intestine, blood platelets, and the brain in rabbits after reserpine administration. They conclude that serotonin in the brain normally exists mainly in bound, inactive form but is liberated by reserpine and rapidly metabolized by amine oxidase. They suggest that the free serotonin is the mediator of the tranquilizing action of reserpine. On the other hand, support for the viewpoint that excess serotonin may be a factor in mental disease is offered by the findings that very small doses of lysergic acid diethylamide facilitate rather than antagonize the action of serotonin [10] and that both reserpine and chlorpromazine antagonize a number of the peripheral actions of serotonin. Furthermore, while peripherally administered serotonin is generally reported to be devoid of central effects, due possibly to the inability of the drug to pass the blood-brain barrier, intraventricular administration of serotonin to cats results in behavioral changes similar in some respects to schizophrenia.[11] While a physiological role for serotonin has by no means been established, the clinical, biochemical, and pharmacological evidence thus far adduced will certainly stimulate further inquiry with a view to determining whether this compound plays a role in normal or abnormal functioning of the brain or whether it has any other functional significance.

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ORGANIZATION SECTION

A. M. A. CITES WINNERS AT NATIONAL SCIENCE FAIR

For the first time, two 16-year-old high school girls will be among the 325 exhibitors in the Scientific Exhibit during the Annual Meeting of the American Medical Association in Chicago, June 11-15, as a result of winning the A. M. A.'s top awards at the National Science Fair in Oklahoma City, May 10-12. As guests of the A. M. A., Lynn C. Dunn of Oklahoma City and Evelyn La Heist of San Diego will be welcomed as the outstanding talents in the basic medical sciences among 213 high school finalists at the fair. Miss Dunn will exhibit her work with "Molds and Algae" and Miss La Heist will display her models depicting the life cycle, effects, and control of the malaria parasite. In addition to the Chicago trip, they were presented citations, signed by Dr. Elmer Hess, A. M. A. President, and Dr. Gunnar Gundersen, Chairman of the Board of Trustees.

Winners of A. M. A. citations at National Science Fair in Oklahoma City: *(left* to *right)* Robert H. Armsby, Washington, D. C.; Lynn C. Dunn, Oklahoma City; Evelyn La Heist, San Diego, Calif.; and Robert B. Nathanson, West Hartford, Conn. The two top award winners will be guest exhibitors in the Scientific Exhibit at the A. M. A.'s Annual Meeting in Chicago, June 11-15.

Two other A. M. A. citations were awarded for honorable mention to Robert B. Nathanson, 15, West Hartford, Conn., for his exhibit entitled "The Effect of Aureomycin on the Encystment and Excystment of the Amoeba," and to Robert H. Armsby, 17, Washington, D. C., a student at Sanford Preparatory School in Hockessin, Del., who displayed a respiration calorimeter.

These awards were made to stimulate interest among talented high school students in a career of medicine and research and to highlight medical society support of local and regional science fairs, which send finalists to the National Fair, conducted annually by Science Clubs of America. The judges for the basic medical science exhibits for the A. M. A. were Dr. Alphonse McMahon, St. Louis, Mo., Chairman, Council on Scientific Assembly; Dr. H. M. McClure, Chickasha, Okla., president, Oklahoma State Medical Association; Dr. Samuel P. Newman, Denver, and Dr. Stanley P. Reimann, Philadelphia, both Council members; Dr. Henry H. Turner, Oklahoma City, past-president, Oklahoma State Medical Association; and Thomas G. Hull, Ph.D., Chicago, Secretary of the Council.

The A. M. A. citations were presented at a special luncheon, for which Science Clubs of America was the host. Dr. Newman made the presentations on behalf of the judging committee. Dr. Alfred R. Sugg, Ada, Okla., past-president, state medical association, was the keynote speaker. Dr. McMahon and the other A. M. A. judges expressed the hope that each physician attending the June Annual Meeting in Chicago will view these award-winning exhibits.

JOINT COMMITTEE ON HEALTH PROBLEMS IN EDUCATION

The Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association held its annual meeting at the National Education Association offices in Washington, D. C., March 12-14, 1956. Meetings of the Committee, which was formed in 1911 and which is one of the oldest Joint Committees of either organization, are alternated between the headquarters buildings of the two parent associations. The major function of the Joint Committee is to consider principles and policies affecting the health of children and youth that are the mutual concern of the two professions.

The chief business of the Committee this year was a critical review of the first draft of its projected new book, "Healthful School Living." This volume, which will probably be published early in 1957, together with the two previous books published by the Committee, "Health Education" (1948) and "School Health Services" (1953), will provide complete coverage by combined medical-education recommendations on all three aspects of the school health program.

Two new pamphlets recently published by the Committee were presented at the annual meeting: "Sleep and Children" (January, 1956) and "Health Aspects of the School Lunch Program" (February, 1956). The addition of these two brochures brings the number of current publications of the Committee to about 20. Like all other publications of the Committee, the two new brochures will be distributed by both the National Education Association and the American Medical Association.

During the 1956 sessions, it was announced that more than 135,000 pamphlets from the sex education series, published by the Committee less than a year ago, have been sold. This series includes five booklets, four of them for children and youth of various ages beginning with the young child and the other an instructional guide for parents, teachers, and youth leaders.

Three new subcommittees were appointed to begin work on the following problems: (*a*) health examination of school personnel, (*b*) pupil transportation, and (*c*) check list for evaluating the school health program. Delbert Oberteuffer, Ph.D., was elected Chairman of the Committee for 1956-1957; Carl Wilzbach, M.D., was named Vice-Chairman; and Fred V. Hein, Ph.D., was reelected Secretary. The Committee adopted the following resolutions:

I. The Joint Committee on Health Problems in Education commends the American Association for Health, Physical Education and Recreation, and the Bureau of Health Education of the American Medical Association for their sponsorship of national conferences aimed at the improvement of health education programs in schools and colleges.

The Fifth National Conference on Physicians and Schools sponsored by the American Medical Association, like its predecessors, has resulted in improved understanding and increased cooperative effort between medical, education and public health personnel as they seek to improve school programs.

The conferences on College Health Education and Health Education for All Teachers sponsored by the American Association for Health, Physical Education and Recreation have been equally productive.

The Joint Committee endorses these endeavors and congratulates the associations on their continuing efforts to encourage and promote sound programs of school health.

II. WHEREAS the most prevalent disease affecting both children and adults in the countries of this continent is dental caries; and

WHEREAS persons living in areas where the drinking water contains small quantities of sodium fluoride are noticeably freer from dental caries; and

WHEREAS sodium fluoride added to water supplies which are deficient in their fluoride content provides the same protection from dental caries as does the naturally-occurring, water-borne fluorides; and

WHEREAS studies have been made of the efficacy of caries prevention by the addition of appropriate amounts of fluoride compounds to public water supplies and the harmlessness of this procedure has been repeatedly shown by such fluoridation of the public water supplies of hundreds of communities many with detailed statistical analyses of the results, all of which are favorable; and

WHEREAS innumerable national, state, and local authoritative organizations have endorsed the fluoridation of public water supplies as a safe public health measure for the prevention of dental caries, among them the American Dental Association, the American Medical Association, the American Academy of Pediatrics, the United States Public Health Service, the American Public Health Association and many others; therefore,

Be it resolved that the Joint Committee on Problems in Health Education of the National Education Association and the American Medical Association

1. Recognizes the value of fluoridation of public water supplies as a means of preventing dental caries through the application of public health principles

2. Recommends the informing of the public by in-school and extra-school educational programs of the value and safety of fluoridation as a caries-prevention measure, and

3. Encourages the public acceptance of fluoridation of public water supplies to reduce the pain, expense, and disfiguration from an excess of carious, filled, and missing teeth.

III. The Joint Committee on Health Problems in Education is cognizant of the national concern for the fitness of children and youth. The Committee is aware that total fitness involves the quality of structure and function of the whole organism and not merely one aspect of it, and believes that schools can make their best contribution to total fitness for young people through well-planned, broadly-based, and expertly-conducted programs of health education, physical education, and recreation. The home, the school and the community all play a significant role in a total fitness program. The Joint Committee recommends that schools in all communities evaluate their programs of health education, physical education, and recreation in terms of sharing appropriately in providing optimum opportunity for the development of total fitness among the youth of the nation.

IV. WHEREAS there is at present a considerable shortage of personnel in many categories of the educational and health professions; and

WHEREAS the demand for such personnel is constantly increasing as the American people become progressively aware of the needs for their services; and

WHEREAS many secondary school students possess excellent potentialities for such careers if these professions could be called to their attention;

Be it therefore resolved:

That the continuing guidance and counseling programs in the secondary schools intensify their programs of information about these professional opportunities; and

That professional organizations now in these fields cooperate with the schools in making available personnel and other resources for such vocational counseling.

STUDY OF PATHOLOGY COVERAGE IN VIRGINIA

Background

During the latter part of 1954 and into 1955, the Virginia Council on Health and Medical Care conducted a study to determine where medical technologists were located and where additional technologists were needed. This study was made at the request of the Virginia Society of Medical Technologists and with the knowledge and "blessing" of the Virginia Society for Pathology. The study was considered a success. It gave the Virginia Society for Pathology an opportunity to observe the Virginia Council on Health and Medical Care in action and to see the type of results that could be achieved through the council's teamwork approach.

A Study Is Born with Purposes

After the meeting of the Virginia Society for Pathology in October, 1955, the Virginia Council on Health and Medical Care was formally requested to undertake a study of pathology coverage in Virginia. The purpose of the study was threefold. First, it was to find out what facilities in Virginia had adequate pathology coverage and which ones needed and wanted additional pathology service. Second, as a continuing part of the study, the council, with the cooperation of the Virginia Society for Pathology, was to try to get the type and extent of pathology coverage desired by the facilities that indicated they needed and wanted help. Third, by giving all hospitals and related facilities an opportunity to have adequate pathology coverage, the Virginia society was, in effect, making a concrete and effective effort to discharge its important responsibility to the public to ensure the best possible pathology coverage for all Virginians. This third item is an important part of the public relations program of the Virginia Society for Pathology. The Virginia Council on Health and Medical Care, which is basically concerned with the improvement and better distribution of medical care, undertook the proposed study with enthusiasm.

Steps Taken in the Study

Each step in the study was taken with the knowledge and approval of the Virginia Society for Pathology. First, a letter explaining the study was written and a simple questionnaire was prepared. These were sent to the facilities licensed by the state health department. They number 141. Of these, 115 are general hospitals with a total of 10,759 beds, 16 are maternity facilities with a total of 180 beds, 3 are tuberculosis sanatoriums with a total of 1,104 beds, and 7 are mental institutions with a total of 14,041 beds. The 141 facilities have a total of 26,084 beds. A copy of the letter, along with a copy of the questionnaire, was sent to the membership of the Virginia Society for Pathology with a covering letter. This was done so that all pathologists would know about the study and cooperate with it. All this correspondence was sent out from the council's office signed by the council's director.

From the original letter, 96 questionnaires were returned. A follow-up letter was sent out and this brought in 35 additional questionnaires. To get the remaining questionnaires in to the council, the services of the president of the Virginia Hospital Association, a number of local physicians, and a pharmacist were used. On March 16, 1956, the final questionnaire was received, making the response 100%. This response is considered most unusual in view of the fact that a 60% participation in such studies is considered good. To some degree, the excellent response is an indication of the desire on the part of many of the facilities contacted to seek additional pathology coverage and also cooperate with an organization like the Virginia Council on Health and Medical Care, whose influence and service touch every section of Virginia.

Statistical Results of the Study

The table that follows summarizes the statistics gathered from the questionnaires. Regardless of the degree of need listed by the facility, it was placed in column 5. Several indicated that they wanted more help but could not support a full-time pathologist at the present time.

Summary of Statistics Gathered from Questionnaires

Type of Hospital	Questionnaires Sent	Questionnaires Returned	Adequately Covered		Need Help		Total No. of Beds
			No.	Beds	No.	Beds	
General hospitals	115	115	98	9,762	17	997	10,759
Maternity facilities	16	16	14	168	2	12	180
Tuberculosis sanatoriums	3	3	3	1,104	0	0	1,104
Mental institutions	7	7	4	5,666	3	8,375	14,041
Total	141	141	119	16,700	22	9,384	26,084

The three mental hospitals indicated that their budgets did not include a pathologist and that an item could not now be added. Still others said that their coverage was adequate but that they would like either more complete or faster service. All facilities that participated in the study are getting some type of coverage, whether they consider it adequate or not.

Follow-Up for the Study

In an effort to help meet the needs of those facilities desiring assistance and to meet the follow-up or continuing objective to the study, the Virginia council has contacted a number of hospitals and clinics asking them specifically what type of help would be of the most assistance to them. In several cases, the council is working to get full-time pathologists for hospitals. In other cases, the council is trying to work out a cooperative arrangement whereby several neighboring hospitals could share a pathologist. In other cases, pathologists presently practicing are being put in touch with facilities in need that are close by and for whom they might be able to provide assistance. The latter plan would provide a more complete utilization of present personnel.

Map

As part of the study, the council secured a large scale map of Virginia, on which all members of the Virginia Society for Pathology are spotted with a symbol of a man. All of the 141 facilities are also spotted on the map, with an indication of the type of facility and the number of beds. The symbol representing these is a building. Those buildings with a green roof are the ones that are adequately covered with pathology service and those with a red roof are the ones needing help. A glance at the map shows clearly what the coverage is in any particular urban or rural area of Virginia. The map will be kept up-to-date with changing conditions.

Conclusions

As far as can be determined, the study of pathology coverage in Virginia is the only one of its kind ever undertaken. It has been an easy study to make and the cost was very little when considering its great importance and its possibilities for bringing better medical care to Virginia's population.

The study was administered by Edgar J. Fisher Jr., director of the Virginia Council on Health and Medical Care in Richmond. He was ably assisted by Drs. Henry G. Kupfer, chairman of the Virginia council's committee on laboratory medicine and professor of clinical pathology at the Medical College of Virginia; John W. Hooker of Danville, president of the Virginia Society for Pathology; George J. Carroll of Suffolk, secretary-treasurer of the Virginia Society for Pathology; and William D. Dolan Jr. of Arlington, councilor from the Virginia Society for Pathology to the American Society of Clinical Pathologists. There were, of course, other pathologists who were consulted. Without the exceptionally fine cooperation offered by the Virginia Society for Pathology, its officers and members, and without the amazing cooperation of the 141 facilities throughout Virginia, it would have been impossible for the Virginia Council on Health and Medical Care to have brought the study to such a successful conclusion. Questions regarding the study of pathology coverage in Virginia may be directed to the Virginia Council on Health and Medical Care, 102 E. Franklin St., Richmond 19, Va.

NEW "MEDICAL HORIZONS" TELEVISION SERIES

"Medical Horizons," the popular television series, will again be presented by Ciba Pharmaceutical Products, Inc., in cooperation with the American Medical Association, beginning Sunday, Sept. 9, at 4:30 p.m. EDT, and each following Sunday over 85 stations of the television network of the American Broadcasting Company.

The show format will remain the same. Don Goddard, veteran newscaster, will return as narrator, and Dr. William T. Strauss will continue to act as medical supervisor.

Commenting on the new 39-week series, T. F. Davies Haines, president of Ciba, said, "We trust that the greatly expanded coverage and continuity of the new series will inspire increased confidence in the American medical profession. We plan to have programs on advances in common everyday problems in medicine as well as on major diseases which as yet have not been fully conquered." Watch your local newspaper for exact time and station in your area.

SECOND STANDARD NOMENCLATURE INSTITUTE

Response to the first regional Standard Nomenclature Institute of the American Medical Association was so overwhelming that another will be held in New York City, July 9-11, at the United Hospital Fund of New York. The three-day short course will offer instruction and advice on ways of using the Nomenclature in the hospital, doctor's office, or clinic. Lectures on anatomy will be given by Edward T. Thompson, M.D., editor, Standard Nomenclature, and on theory by Adaline C. Hayden, C.R.L., associate editor. Practice periods in coding also will be given on Monday and Tuesday evenings. Applications should be sent to Mrs. Hayden at A. M. A. Headquarters, 535 N. Dearborn St., Chicago 10.

DR. HOLLAND APPOINTED COUNCIL SECRETARY

Dr. B. Dixon Holland, who will retire soon as a colonel in the U. S. Army Medical Corps, has been appointed by the Board of Trustees of the American Medical Association as Secretary of the Council on Industrial Health. On or about July 15, he will fill the post left vacant by the recent death of Dr. Carl M. Peterson. Dr. Holland is presently serving as medical director of the Army Federal Civilian Employees' Health Service and as chief of preventive medicine at Aberdeen Proving Ground, Maryland. A native of Denton, Texas, he was graduated from the University of Texas Medical School at Galveston in 1934.

FEDERAL MEDICAL LEGISLATION

Second Session, 84th Congress

Medical and Dental Expense Deductions

Congressman Gubser (R., Calif.), in H. R. 9545, would amend the Internal Revenue Code to provide that amounts paid for the medical and dental care of children who have not attained the age of 6 years shall be deductible in computing income tax, without regard to the present limitation, and that such expenses can be deductible only when they exceed 3% of adjusted gross income. This measure was referred to the Committee on Ways and Means.

Federal Aid for Education of Nurses

Congressman Lane (D., Mass.) proposes, in H. R. 9553, "to provide a program of grants and scholarships to encourage education and training in the field of nursing." The bill would authorize such sums as are necessary to provide states with matching grants, not to exceed 50% of the entire cost of (1) assisting schools of nursing to maintain and increase enrollment and to improve and expand their curriculums and (2) providing scholarships to defray a part or all of the cost of tuition, books, equipment, and maintenance. A minimum grant of $200,000 would be made to each state. The surgeon general of the Public Health Service would administer the program. This bill was referred to the Committee on Interstate and Foreign Commerce.

Presumption of Service-Connection for Idiopathic Convulsive Seizures

Congressman Granahan (D., Pa.), in H. R. 9653, would amend the Veterans Regulations "to provide that idiopathic convulsive seizures manifesting a 10 per centum degree of disability or more within six months from the date of separation from active service shall be conclusively presumed to" be service-connected. This bill was referred to the Committee on Veterans' Affairs.

Transfer of Veterans Administration Hospitals

Congressman Weaver (R., Neb.), in H. R. 9729, Long (D., La.), in H. R. 9814, and Teague (R., Calif.), in H. R. 9923, have introduced similar measures that would prohibit the transfer of veterans hospitals to other government agencies without transmitting such proposals to Congress with reasons therefor. Transfer could not be made before the expiration of 90 days of continuous session of Congress following a transmittal date. Either of the two Houses of Congress could block such a transfer. Congressman Edmondson (D., Okla.), in H. R. 9807, prohibits transfer or closing of VA hospitals and regional offices without giving Congress an opportunity to block such action. All of these measures were referred to the Committee on Veterans' Affairs.

National Library of Medicine

Senators Hill (D., Ala.) and Kennedy (D., Mass.), in S. 3430, would establish a National Library of Medicine to take over the publications and functions of the Armed

Prepared by the Washington Office of the American Medical Association.

Forces Medical Library (previously the Surgeon General's Library), to be administered by a board of regents. The board would be composed of the surgeons general of the Army, Navy, Air Force, and Public Health Service and the librarian of Congress, and 12 individuals appointed by the President, to be confirmed by the Senate. The appointed members would be chosen from fields such as medical research, medical education, medical practice, and medical librarianship; preventive medicine and public health; dentistry; hospital administration; and pharmacy and pharmaceutical production. The director would be appointed by the board without regard to Civil Service laws. The library could accept and administer gifts and bequests. This measure is a substitute for those submitted by the Hoover Commission and previously reported. It was referred to the Committee on Labor and Public Welfare. At hearings, majority support was given to placing the library in the Department of Health, Education, and Welfare.

Commission on Nursing Services

Senator Smith (R., N. J.), in S. J. Res. 158, has introduced a measure that would establish a Commission on Nursing Services, identical to Congresswoman Bolton's H. J. Res. 485, and similar to H. J. Res. 171 and S. J. Res. 56, all previously reported. This measure was referred to the Committee on Labor and Public Welfare.

Three-Year Presumption for Chronic and Tropical Diseases

Congressman Buckley (D., N. Y.), in H.R.9169, would increase from one year to three years that period of time in which a chronic or tropical disease, becoming manifest to a degree of 10% or more, would be deemed to have been service incurred. This bill was referred to the Committee on Veterans' Affairs.

Federal Aid for Medical Education

Congressman Mack (D., Ill.), in H.R.9186, has introduced a bill to authorize federal aid to medical education. It is identical with S.1323, by Senator Hill (D., Ala.), which was previously reported. H.R.9186 was referred to the Committee on Interstate and Foreign Commerce.

Temporary Disability Benefits for D. C. Employees

Congressman Broyhill (R., Va.) in H.R.9447, would establish a temporary disability insurance program for employees in the District of Columbia, similar to programs in New York, New Jersey, Rhode Island, and California. Disability would be defined as "inability of an individual as a result of his physical or mental illness, disease, or injury to perform his most recent, customary or reasonable similar work." Employers could purchase insurance, become a self-insurer and post security, or, if their payrolls were small, could insure through a public insurance fund operated by the government of the District of Columbia. Benefits would be one-half of the individuals average wage, $36 maximum and $12 minimum (if the average wage is $12, the benefit would be the same as the wage). Benefits would be payable up to 26 weeks within a 52-week period. This measure was referred to the Committee on the District of Columbia.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

VERIFICATION OF 1956 DIRECTORY LISTING

During the past week, verification cards were sent out to all hospitals approved for residency training, on which were recorded the data on residency programs to be published in the 1956 Directory of Approved Internships and Residencies. This additional check has been developed to eliminate, as far as possible, inaccuracies in the lists of approved services.

The data included on the verification card are those submitted by the hospital in the Annual Report on Internships and Residencies for this year. Hospital administrators are urged to check these cards carefully and return them, with corrections, prior to June 15, if the data as recorded are inaccurate. In the event that the data on the verification card are accurate, the card need not be returned. The cooperation of hospital administrators and chiefs of services in checking these verification cards will make possible the publication of more complete and accurate information in the 1956 Directory.

COUNCIL ON MENTAL HEALTH

The following report is a short progress note prepared and presented at the 112th Annual Meeting of the American Psychiatric Association, Chicago, April 30-May 4, 1956, by Dr. Leo H. Bartemeier, who is chairman of the board of trustees of the Joint Commission on Mental Illness and Health, Inc., as well as Chairman of the Council on Mental Health.

So far the Joint Commission has identified three specific areas in which task forces are expected to start work in June, 1956. These are a study of the mental health processes in schools, a study of patterns of patient care in both hospitalized and nonhospitalized populations, and a survey of the status of research in the mental health field. Other task force groups will be developed as the specific areas where study is most needed are defined.

R. J. PLUNKETT, M.D.
Secretary.

JOINT COMMISSION ON MENTAL ILLNESS AND HEALTH

I have been asked to bring you up-to-date on the present status of the Joint Commission on Mental Illness and Health. I know that most of you are familiar with the developmental history of the Commission, but, for those of you who are not, perhaps I should sum up the

Commission's history briefly. About two and a half years ago a small group of American Psychiatric Association members led by our then president, Dr. Kenneth Appel, and the members of the Council on Mental Health of the American Medical Association held a series of informal meetings with a view to finding out how the American Psychiatric Association and the American Medical Association might best combine their efforts to accomplish something that would be eventually of value in the field of mental illness and health. The consensus of these discussions was that what was urgently needed was a new over-all review of the present status of the field and a search for ways in which our present approaches could be improved. This led to the setting up of a Joint Commission between the two organizations to discuss methods of carrying out such a study. The proposal received full and formal recognition by the official bodies of the American Psychiatric Association and the American Medical Association.

As deliberations proceeded, two significant developments occurred. First, it was recognized that, in an undertaking that was conceived as such an all-embracing task, many additional organizations whose work was closely tied in with the problem of mental illness and health needed to be included because of the very real contributions they could make. Some 20 such organizations were invited to participate, and they accepted. The Commission was then legally incorporated as a nonprofit organization in late 1955. The organizations now participating are in the public record.

The second major significant development came about entirely apart from the deliberations of the Commission members when it became known that in federal government and congressional circles there had been going on for some two or three years a parallel to the Commission members' thinking. In both houses of Congress and in both major political parties there had been an increasing awareness of the need for a survey of the nation's mental health resources, both because of the acuteness of the problem itself and because of the associated problem it created in the nation's manpower loss.

The recognition of this need, strongly led by Sen. Lister Hill of Alabama and Rep. Percy Priest of Tennessee, culminated in the passage of an act providing funds for a mental health study by organizations outside of the government labeled as the Mental Health Study Act of 1955. As you may know, this act passed without one dissenting vote in both houses of Congress.

The Joint Commission applied for these funds through the National Institute of Mental Health and was granted $250,000 to start work in January of this year. We all know the many difficulties that lie between seeing the need and desirability of such a tremendous study and its actual accomplishment. Nevertheless, under the capable direction of Dr. Jack Ewalt as principal research investigator, with headquarters offices in Cambridge, Mass., great strides toward our final goal are being made.

The staffs utilizing several intelligent advisory committees, has now produced an over-all research model for the work to be done. This research model concentrates the attention of the study on people and what happens to them in our society. Starting with considerations of a person's biological, psychological, and cultural background, the model envisions a study of individuals as they relate themselves to the critical stages of development from birth through preschool, school, and work periods, and as they relate themselves to family, church, marriage, and other cultural factors in our society. In these areas the model also envisions a study of these institutions to find out the factors in them that contribute toward or inhibit the development of an effective emotionally functioning person.

For those persons who do not achieve this, the model relates itself to a study of the nonprofessional helping agencies in the community, to find out what they actually achieve; a study of the professional people and agencies in the community, to find out what they achieve after the person has arrived at the status of a "patient"; and, finally, of course, to a study of the hospitalized patient situation. We hope to study all of these situations both horizontally and in depth.

We know that we can reach and study what happens to people at the contact points I have mentioned. Perhaps one of the most difficult tasks of the Commission, however, is going to be the discovering of methods to approach the great mass of emotionally suffering people whose problems never reach any helping person or agency.

We know, or we think we know, that there are vast numbers of such persons in America, perhaps hundreds of thousands, who, for long periods of their lives, go through agonizing mental and emotional suffering without help from any source. We do not know their number, who or where they are, but we do need to know how these people can be found and brought to realize that they can be helped. On the other hand, and more hopefully, we know there are vast numbers of people, perhaps millions, who suffer the same emotional storms and stresses and who without professional or other outside help finally gain the calmer waters of emotional balance and happiness. Again, we do not know their number, or who and where they are. Also we do not know how they do this. It will be helpful to the study, and to people generally, if we can explore and find out how these people help themselves.

I am sure with respect to these last areas I mentioned that you all have suggestions and ideas, even pet ideas, that have never been exposed to the test of public trial. Write to us, tell us about them, they will be warmly received. We will give them full consideration in our Commission discussion groups. In the meantime, if you have other questions about the Commission's work, we will be glad to answer them, certainly with sincerity, and to the best of our ability.

MEDICAL NEWS

CALIFORNIA

The Original Gold-Headed Cane.—For the 20th awarding of the Gold-Headed Cane by the University of California Medical School, San Francisco, Dr. Charles M. Wilson Moran, past-president of the British Medical Association and personal physician to the late George VI and Sir Winston Churchill, will bring with him from the Museum of the Royal College of Physicians the original Gold Headed Cane that has been carried by a series of eminent physicians in England. Lord Moran's visit, especially for these ceremonies, was suggested and made possible by Dr. William J. Kerr, professor emeritus of medicine, who originated the Gold-Headed Cane Ceremonies at the University of California, through which the award is given to that student in the senior class who possesses to the highest degree—in the opinion of his classmates and of the faculty of the department of medicine—the qualities of the "true physician." The award will be given on June 4 at the Morrison Auditorium in Golden Gate Park, where the senior class will gather for these ceremonies and the administration of the Hippocratic oath. The faculty, the senior class, and members of the medical profession are cordially invited.

DISTRICT OF COLUMBIA

Society News.—More than 200 physicians from 20 states are expected to attend the 34th annual meeting of the Association of Former Internes and Residents of Freedmen's Hospital at the hospital in Washington, D. C., June 5-7. The scientific meetings and exhibits will be held in the new air-conditioned School of Architecture and Engineering of Howard University.——The Tropical Medicine Association of Washington, D. C., was organized on Jan. 20. Three seasonal meetings are scheduled. *Ad hoc* gatherings will be called as visiting experts may become available. Membership is open to all residents in and near Washington, D. C., who are professionally interested in tropical medicine. Officers for the coming year are: president, Justin M. Andrews, Sc.D., Atlanta, Ga.; vice-president, Donald B. McMullen, Sc.D., Oklahoma City; and secretary-treasurer, Dr. Louis L. Williams Jr., Chevy Chase, Md. The speaker at the organizational meeting, Dr. Elmer G. Berry, Ph.D., Bethesda, Md., discussed schistosomiasis research and control demonstration in Egypt.

ILLINOIS

Clinics for Crippled Children.—The University of Illinois division of services for crippled children has scheduled the following clinics to which any private physician may refer or bring children for consultative services:

June 6, Hinsdale, Hinsdale Sanitarium and Hospital; Rock Island (cerebral palsy), Foss Home, 3808 Eighth Ave.
June 8, Chicago Heights (cardiac), St. James Hospital.
June 12, Peoria, Children's Hospital; East St. Louis, Christian Welfare Hospital.
June 14, Elmhurst (cardiac), Memorial Hospital of DuPage County; Springfield, St. John's Hospital.

Chicago

Panel on Diabetes.—The Chicago Diabetes Association announces that its annual spring meeting, June 7, will be sponsored by the lay society. The meeting, open to the public without admission charge, will be held at 8:15 p. m. in the Murphy Memorial Auditorium, 50 E. Erie St. A panel discussion will be offered with the following participants:

Charles H. Best, Toronto, Canada, Past, Present, and Future of Diabetes.
Francis D. W. Lukens, Philadelphia, Oral Insulin Substitutes.
Alexander Marble, Boston, Complications of Diabetes.
Blair Holcomb, Portland, Ore., Living with Diabetes.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

MARYLAND

Alumni Day.—The Medical Alumni Association of the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, will hold its annual Alumni Day at the University Hospital, Baltimore, and the school of medicine June 7. The annual Alumni Honor award and gold key will be presented to Dr. Joseph Nataro, Newark, N. J., of the class of 1925. The evening's activities will be climaxed by the annual alumni banquet held in honor of the class of 1956.

MICHIGAN

Clinical Research Symposium.—The Northville State Hospital will present its second Clinical Research Symposium June 6, with Dr. Philip N. Brown, superintendent, as moderator. The program will open with "Atropine Toxicity Therapy: Historical Background and Future Research" by Dr. Gordon R. Forrer, clinical director of the hospital, and will close with "Atropine Toxicity Therapy: Experiences of Use in Private Practice" by Dr. Richard D. Goldner, Saginaw. Discussion groups will be conducted from 3:50 to 5 p. m. by Dr. Forrer (research), Dr. Goldner (private practice), and Dr. Jacob Miller, chief, intensive treatment unit at the hospital, who will give clinical demonstrations, case presentations, and a discussion of techniques and procedures during the program.

PENNSYLVANIA

Speech and Hearing Center.—A speech and hearing center in the Hospital of the University of Pennsylvania, Philadelphia, has been established by the department of physical medicine and rehabilitation under a grant from the Office of Vocational Rehabilitation of the U. S. Department of Health, Welfare, and Education. Patients will be accepted on referral from physicians and local health agencies and will be seen by appointment. As the program expands, it is expected to coordinate the services of the state cleft palate clinic, located in the Children's Hospital of Philadelphia; the United Cerebral Palsy Center at Chestnut Hill; and the speech clinic division of the Psychological Clinic of the University. The speech and hearing center has been established under the auspices of the university's rehabilitation commission.

Philadelphia

Society News.—Newly elected officers of the Philadelphia Allergy Society include Dr. Philip M. Gottlieb, president; Dr. Edmund E. Ehrlich, vice-president; and Dr. Eugene A. Hildreth, secretary-treasurer.——The Philadelphia chapter, Institute of Radio Engineers Professional Group on Medical Electronics, and the Philadelphia section of the institute will present a symposium, "Electrodes and Amplifiers & Biological Research," June 8 in the University of Pennsylvania Physical Sciences Building (S. E. corner, 33rd and Walnut streets). The session will include "A Useful Sodium Ion Glass Electrode" by Dr. George Eisenman, Dr. Donald O. Rudin, and James U. Casby, B. S., Eastern Pennsylvania Psychiatric Institute, Philadelphia, and a panel discussion on bioelectric measuring techniques.

WISCONSIN

Governor's Geriatric Conference.—The Governor's Conference on an Aging Population will convene at the University of Wisconsin, Madison, June 6-8, with the cooperation of the State Medical Society of Wisconsin and 27 other organizations. Included in the tentative areas of discussion are medical and health care, community planning, education, use of leisure time, the older worker, economic security, the church and the older person, group living and care, housing, community contributions by the aging, and laws, legislation, and policy.

GENERAL

Michael Reese Staff Alumni Reunion.—The annual reunion of the Michael Reese Hospital house staff will be held in Chicago June 13. The program will include morning clinics and lunch at Michael Reese Hospital and a banquet at the Furniture Club, preceded by a cocktail party at 6:30 p. m. Former house staff and present attending staff members are urged to make reservations at once through the Michael Reese Hospital Alumni Association, 29th Street and Ellis Avenue, Chicago 16.

Fellowship in Cardiology.—The Southcentral Alaska Heart Association has established a cardiac research fellowship in the department of medicine of the University of Washington School of Medicine, Seattle, beginning in July. The fellowship, which involves a $5,000 grant for this year, will be under the direction of Dr. Robert A. Bruce, associate professor of medicine and head of the department of cardiology at the university. The fellowship is being granted to an experienced cardiac researcher.

Meeting of Genitourinary Surgeons.—The American Association of Genito-Urinary Surgeons will hold its 67th annual meeting June 4-6 at Oyster Harbors, Osterville, Mass. A symposium on cryptorchism is scheduled for Monday and a symposium on remedial renal hypertension for Tuesday. The Tuesday morning session will open at 8:30 with a movie, "The Potential Use of Vibration for the Disintegration of Calculi" by Dr. Howard I. Suby, Boston. Presentations by invitation will include "Bladder Dysfunction Secondary to Meningocele Repair in Infancy, Improved Five to Fifteen Years Later by Intraspinal Surgery" by Dr. James B. Campbell, New York, and "The Endocrine Kidney" by Dr. Kendall Emerson Jr., Boston.

Medical Women's Association.—The American Medical Women's Association will hold its annual meeting June 7-10 at the Blackstone Hotel, Chicago, under the presidency of Dr. Esther C. Marting, Cincinnati. On Saturday at 12:15 p. m. Dr. Carroll C. L. Birch, New Delhi, India, will present the Woolley Memorial Lecture, "Medical Problems of India." A cocktail party at 6 p. m. will precede the inaugural banquet, 7 p. m., at which Dr. Camille Mermod, Newark, N. J., will assume the presidency. Luncheon Sunday, 12:15 p. m., will be preceded and followed by a symposium, "Occupational Health of Women." The topics will include: Sickness and Absenteeism; Obstetrical and Gynecological Problems; Accidents and Disabilities; Emotional Problems; Human Relations and Counseling; and the Dual Role of Homemaker and Wage Earner. The luncheon speaker, Wilma T. Donahue, Ph.D., University of Michigan, Ann Arbor, will have as her topic "The Older Woman."

Meeting of Tuberculosis Physicians.—The American Academy of Tuberculosis Physicians will hold its annual meeting June 9 at the Palmer House, Chicago, under the presidency of Dr. Harry Shubin, Philadelphia. The morning session will open with "Comparison Between the Degree of Cutaneous Reaction and the in Vitro Toxicity of Tuberculin from Peripheral Blood Leucocytes" by Dr. Cutting B. Favour, Palo Alto (Calif.) Medical Research Foundation, and close with "The Conversion of a Tuberculous Unit into a Geriatric Hospital" by Dr. Jacob S. Sherson, Malvern, Pa. The presidential address will be delivered at the luncheon, 12:15-2 p. m., where the guest speaker will be Dr. Harold G. Trimble, Oakland, Calif., whose subject will be "The First Line of Defense in Tuberculosis." The afternoon session will open with "An Epidemic of Tuberculosis" by Dr. Stefan Grzybowski, department of health, office of the deputy minister, Toronto, Canada, and close with "Corppins' Extended as Individual Simple Disposable Tests with Tuberculin, Histoplasmin, Coccidioidin, Blastomycin, and Other Allergens" by Dr. Harry J. Corper, Denver, and Dr. Shubin.

American Rheumatism Association.—The annual meeting of the American Rheumatism Association will convene at the Conrad Hilton Hotel, Chicago, June 8-9. The presidential address will be delivered by Dr. Charles L. Short, Boston, Friday, 2:15 p. m. "The Differential Diagnosis of Ankylosing Spondylitis" by Dr. James Sharp, Manchester, England (by invitation), will precede a panel discussion, "Gout: Questions and Answers on the Pathogenesis, Diagnosis and Treatment," which will conclude the Friday afternoon session. The meeting Saturday morning will be held in conjunction with the Council on Rheumatic Fever and Congenital Heart Disease. At luncheon Saturday, 12:45-2 p. m., Dr. L. Maxwell Lockie, Buffalo, will present "The American Rheumatism Association and the Food and Drug Administration," and Dr. Currier McEwen, New York, and Floyd S. Daft, Ph.D., Bethesda, Md., will have as their topic "Training Grants and Traineeships in Arthritis." The luncheon will be followed by a panel discussion, "The Teaching Collection of Lantern Slides on the Pathology of Arthritis and Rheumatism." In all, 29 papers will be presented and 41 will be read by title.

Angiologists Meet in Chicago.—The International Society of Angiology, North American chapter, will hold its fourth scientific meeting June 9 at the Conrad Hilton Hotel, Chicago, under the presidency of Dr. Alton Ochsner, New Orleans. The morning session will open with "Alterations in Digital Blood Flow Resulting from Restoration of Vascular Continuity in the Treatment of Aneurysms and Occlusive Disease" by Dr. Oscar Creech Jr. (by invitation) and Dr. Michael E. De Bakey, Houston, Texas, and will close with a panel discussion, "Present Status of Open Heart Surgery," with Dr. Wilfred G. Bigelow, Toronto, Canada, as moderator, and the following invited participants: Dr. S. Gilbert Blount Jr., Denver, Dr. John W. Kirklin, Rochester, Minn., and Dr. C. Walton Lillehei, Minneapolis. The afternoon session will open with "Analysis of 130 Consecutive Grafts of Major Arteries" by Drs. Fay A. Lefevre, Alfred W. Humphries (by invitation), and Victor G. De Wolfe (by invitation), Cleveland, and will close with "The Problem of Perforator Localization in Primary Varicosis" by Drs. Theodore B. Massell and E. Craig Heringman (by invitation), Los Angeles. The president's address, "The Training of the Vascular Surgeon," will be delivered at the annual banquet.

Meeting on Sterility.—The 12th annual meeting of the American Society for the Study of Sterility will be held at the Conrad Hilton Hotel, Chicago, June 8-10, under the presidency of Dr. Somers H. Sturgis, Boston. Dr. Pierre-Hubert de Watteville of Geneva, Switzerland, will deliver the Ayerst Lecture, "Psychological Factors in the Treatment of Marital Sterility," on Sunday. He will also present a paper at one of the scientific sessions on "Day to Day Variations in Urinary Hormone Level During the Normal Menstrual Cycle" and will conduct a round table on "Tests for the Detection of Ovulation." Elwin L. Willett, Ph.D., Madison, Wis., research director of the American Foundation for the Study of Genetics, will talk on "Evaluation of Bull Fertility." Dr. Richard J. Blandau, Seattle, will present "Recent Observations on Ovulation in the Rat" and John MacLeod, Ph.D., New York, "Metabolism of Human Spermatozoa." Luncheon round-table conferences (12:30-2 p.m.) will include the following subjects:

Tests for the Detection of Ovulation.
How and Where to Train Young Men to Investigate and Treat Infertility.
The Cervix.
Psychogenic Infertility.
Visual Methods of Diagnosis in Infertility.
Artificial Insemination.
Endocrine Aspects of Infertility: Failure of Endometrium and Anovulatory Problems.
Male Infertility Standards.
Treatment of Male Infertility.
Surgery in Male Infertility.

Chest Physicians Meet in Chicago.—The 22nd annual meeting of the American College of Chest Physicians will convene at the Hotel Sherman, Chicago, June 7-10. The scientific session will open at 8 p. m., with the first Louis Mark Memorial Lecture, "What Can the Public Health Service Contribute to the Private Practice of Medicine," by Dr. Leroy E. Burney, assistant surgeon general, U. S. Public Health Service, Washington, D. C., which will be followed by a symposium on carcinoma. Friday morning will be devoted to symposiums on cardiopulmonary physiology and on congenital cardiovascular disease. The symposium on pulmonary fibrosis, 2 p. m., will be followed at 3:15 p. m. by "Tuberculosis and Related Problems" (part 1); parts 2 and 3 will be given Saturday at 10 a. m. and 2 p. m. respectively. Fireside conferences Friday, 8:15 p. m., will encompass 27 topics. Saturday morning there will be a symposium on acquired cardiovascular disease and Saturday afternoon a symposium on fungus diseases. Hypertension and other

cardiovascular problems will be considered at 8:55 a. m. Sunday and current problems in respiratory disease at 10:30 a. m. The sessions will close Sunday afternoon with a symposium on coronary artery disease, 2:30 p. m. Four postgraduate seminars have been scheduled for the day preceding the scientific program; six round-table luncheons on Friday, Saturday, and Sunday; and a motion picture program of recent films dealing with diseases of the chest will be shown concurrently with the scientific program on these three days. The annual convocation (formal) at 6 p. m. and a cocktail party sponsored by the Panray Corporation, New York City, at 7 p. m. will precede the annual president's banquet.

American Therapeutic Society.—The 57th annual meeting of the American Therapeutic Society will be held at the Sheraton-Blackstone Hotel, Chicago, June 7-10. The president, Dr. Fred E. Ball, Chicago, will respond to the opening address of welcome Friday, 9 a. m., by Dr. Maurice M. Hoeltgen, president, Chicago Medical Society. The president's address, "The Present Shortage of Hospital Nursing Personnel and the Responsibility of the Doctor," will be delivered by Dr. Ball Friday afternoon. The fifth annual Lewis Harvie Taylor Lecture, "Hepatitis: Problems in Epidemiology and Treatment," will be delivered Friday by Dr. Richard B. Capps, associate professor of medicine, Northwestern University Medical School, Chicago. The Friday session will close with a panel on respiratory disease, moderated by Dr. George E. Wakerlin, Chicago. The panel members, all of whom will participate by invitation, will be Drs. Albert H. Andrews Jr., Paul H. Holinger, Karl H. Pfeutze, Harry F. Dowling, and Robert J. Jensik, all of Chicago. Saturday morning Dr. Eugene M. K. Geiling, Frank P. Hixon Distinguished Service Professor of Pharmacology and chairman of the department, University of Chicago School of Medicine, will present "The Value of the Radioactive Isotopes in Pharmacologic Research." Dr. Geiling will be given the second Oscar B. Hunter Memorial Award in Therapeutics for his work in the use of tag elements in pharmacology. Saturday afternoon will be devoted to a discussion of "Medical Horizons—A Look Into the Future." The president's reception, 7:30 p. m., will precede the annual banquet, 8 p. m., at which Dr. LeRoy H. Sloan, Chicago, will serve as toastmaster. Mr. John E. Reid, director, John E. Reid and Associates, Chicago, the speaker of the evening, will have as his subject "The Lie-Detector." Brunch is scheduled at 12 noon Sunday at the "Top of the Rock" in the Prudential Building. Twenty-three physicians will participate by invitation in the scientific sessions.

North and South Dakota Medical Meeting.—In celebration of 75 years of Dakota medicine, the North Dakota State Medical Association (Dr. David J. Halliday, Kenmare, president) and the South Dakota State Medical Association (Dr. F. Daniels Gillis, Mitchell, president) will hold a joint meeting in the Civic Arena at Aberdeen, S. D., June 2-6. One of the features of the session will be a cancer forum moderated by Dr. Leonard W. Larson, Bismarck, N. D., Trustee of the American Medical Association, with the following participants: Drs. Lauren V. Ackerman, St. Louis, Roger A. Harvey, Chicago, and Arnold S. Jackson, Madison, Wis. Presentations by other out-of-state speakers will include:

Diseases of the Thyroid, George Crile, Cleveland.
Acute Obstructive Supraglottic and Infraglottic Laryngitis, Alden H. Miller, Los Angeles.
Management of Cephalopelvic Disproportion, William F. Mengert, Chicago.
Dermatologic Use of Steroids, Francis W. Lynch, Minneapolis.
Tuberculosis and the Physician in General Practice, Jay A. Myers, Minneapolis, and Walter L. Palmer, Chicago.
Diabetes Mellitus with a Discussion of the Newer Types of Insulin, Edward H. Rynearson, Rochester, Minn.
Evaluation of Newer Surgical Techniques for Congenital Malformations of the Heart, Paul Adams, Minneapolis.
Foot Problems Amenable to Surgical Treatment, Markham B. Coventry, Rochester, Minn.
Surgical Treatment of Hydronephrosis, Frederic E. B. Foley, St. Paul.
The Respirator Center and Rehabilitation, William A. Spencer, Houston, Texas.
Precancerous Lesions of the Colon and Rectum, Walter A. Fansler and Charles A. Neumeister, Minneapolis.
Postoperative Psychoses, Ernest M. Hammes Jr., St. Paul.

The annual banquet will be followed by a public meeting, at which Dr. Elmer Hess, Erie, Pa., President, American Medical Association, will deliver an address. The banquet speaker Monday will be Dr. Dwight Murray, Napa, Calif., President-Elect of the A. M. A. The North Dakota Diabetes Association will hold a luncheon Tuesday noon, at which Dr. Rynearson will discuss diabetes.

Proctologists Meet in Detroit.—The 55th annual meeting of the American Proctologic Society will convene at the Hotel Statler, Detroit, June 6-9. Wednesday will be devoted to a basic science program, moderated by Dr. Louis J. Hirschman, Traverse City, Mich., emeritus professor of proctology, Wayne University College of Medicine, Detroit. On Thursday at 12:30 p. m. a luncheon symposium, "Extramedical Problems," moderated by Dr. Louis A. Buie, Rochester, Minn., member of the Judicial Council, American Medical Association, and Chairman of the Council on Constitution and Bylaws, will include the following discussions by members of the A. M. A. staff:

Medical Legislative Picture, Mr. Richard Van Buskirk, Executive Secretary of the Council on Medical Legislation.
Medicolegal Problems, George E. Hall, J.D., Executive Secretary, Council on Constitution and Bylaws.
Medical Press Relations and Public Relations, Mr. John L. Bach, Director, Press Relations.

Symposiums will also be offered on "Postoperative Diarrheas and Infections" (moderator, Dr. Neil W. Swinton, Boston) and "Physical Agents Used in the Treatment of Anorectal Diseases" (moderator, Dr. J. Peerman Nesselrod, Evanston, Ill.). Guest papers will include:

Diverticulitis of the Colon—Choice of Operative Procedures, Henry K. Ransom, Ann Arbor, Mich.
One Stage Total Colectomy for Ulcerative Colitis, Lawrence S. Fallis, Detroit.
Traction Sigmoidoscope for Diagnosis and Therapy, Alois E. Moore, San Diego, Calif.
Fifteen-Year Survey of the Management of the Bladder Following Abdominoperineal Proctosigmoidectomy and Other Bowel Surgery, Lowrain E. McCrea, Philadelphia.
Lieut. Commander Robert M. Dimmette, Bethesda, Md., will present a guest discussion on "The Role of the Proctologist in the Diagnosis of Schistosomiasis Mansoni by Sigmoidoscopy and Rectal Biopsy."

Social events will include a cocktail party, Wednesday, 5-6:30 p. m. (for all members and guests and their wives); a reception, 6 p. m., and banquet (formal), 7 p. m., Saturday; and, for the ladies, a visit to the Ford factory and museum, Thursday, and a tour of Detroit Friday.

CANADA

Indian Rehabilitation Program.—An experiment in the rehabilitation of young Indians who have been treated for tuberculosis was recently undertaken by the Charles Camsell Institute in Edmonton, Alberta, under the sponsorship of the federal government. Since traditional Indian occupations are too strenuous for former tuberculosis patients, the new program deals with vocational training in the city after discharge from the hospital. At the time of report 9 young men had been placed in one rehabilitation boarding home and 11 young women in another.

FOREIGN

Congress of Health Technicians.—The fifth International Congress and Exposition of Health Technicians will be held in Paris, France, June 5-8. The questions discussed will be Recent Developments in Surgery, Medicine, and Pharmacy: Their Influence on Hospital Function and Laboratory Techniques; Architecture and Equipment of Hospitals; Health Education; Administration and Its Techniques; and Humanization of the Hospital. Information may be obtained from the Secretariat General: 37, rue de Montholon, Paris 9.

CORRECTIONS

Diagnosis and Treatment of Chronic Pericarditis by Pericardial Biopsy.—In THE JOURNAL, May 19, 1956, page 188, the title of the paper, "Diagnosis and Treatment of Chronic Pericarditis by Pericardial Biopsy," by William L. Proudfit, M.D., and Donald B. Effler, M.D., appeared with the word "Cardiac" in place of "Chronic."

Chicago North Side Water Tower.—In THE JOURNAL, April 28, page 1478, the legend under the picture of the Chicago Water Tower stated that the tower marked the northern limits of the great Chicago fire of 1871. Mr. L. S. Graves of Davenport, Iowa, wrote that the legend was in error and that the fire extended as

far north as Oak Street. Mr. Graves was told that THE JOURNAL obtained the legend for this picture from the Chicago Convention Bureau, which on receipt of a letter from Mr. Graves checked with the Chicago Historical Society and was told that the northern limit of the fire was at Fullerton Avenue.

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Various Centers. June 19-20 (Parts I and II); September 4-5 (Part I). Candidates may file applications at any time but they must be received at least six weeks before the date of the examination for which application is made. New candidates should apply by formal registration; registered candidates may notify the board, indicating desired location, date and candidate number. Ex. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia 4.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 19-21. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

ARKANSAS:* *Examination.* Little Rock, June 14-15. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Examination.* San Francisco, June 25-28. Exec. Sec., Mr. Wallace D. Thompson, 1020 N St., Room 536, Sacramento.

COLORADO:* *Examination.* Denver, June 12-13. Exec. Sec., Miss Beulah H. Hudgens, 831 Republic Bldg., Denver 2.

CONNECTICUT:* *Examination.* Hartford, July 10-12. Sec., Dr. Creighton Barker, 160 St. Ronan St., New Haven.

DELAWARE: *Examination.* Dover, July 10-12. *Reciprocity.* Dover, July 19. Sec., Dr. Joseph S. McDaniel, 229 S. State St., Dover.

FLORIDA:* *Examination.* Miami Beach, June 24-26. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

GEORGIA: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 111 State Capitol, Atlanta 3.

IDAHO: *Examination, Reciprocity and Endorsement.* Boise, July 9-11. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Examination and Reciprocity.* Chicago, June 19-21 and Oct. 9-11. Supt. of Regis., Mr. Frederic B. Selcke, Capitol Building, Springfield.

INDIANA: *Examination.* Indianapolis, June. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

IOWA:* *Examination.* Iowa City, June 11-13. Exec. Sec., Mr. Ronald V. Saf, 310 Bankers Trust Bldg., Des Moines.

KANSAS: *Examination and Reciprocity.* Kansas City, June 6-7. Sec., Dr. Lyle F. Schmaus, 872 New Brotherhood Bldg., Kansas City.

KENTUCKY: *Examination.* Louisville, June 4-6. Sec., Dr. Russell E. Teague, 620 S. Third St., Louisville 2.

LOUISIANA: *Regular. Examination and Reciprocity.* New Orleans, June 5-7. Dr. E. H. Lawson, 930 Hibernia Bank Bldg., New Orleans. *Homeopathic.* Subject to call. Sec., Dr. F. H. Hardenstein, 903 Pere Marquette Bldg., New Orleans 12.

MAINE: *Examination and Reciprocity.* Augusta, July 10-11. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, June 19-22. Sec., Dr. Lewis P. Gundry, 1211 Cathedral St., Baltimore.

MARYLAND: *Homeopathic. Examination.* Havre de Grace, June 25-27. Sec., Dr. Robert H. Reddick, R.D. #2, Cambridge.

MASSACHUSETTS: *Examination.* Boston, July 10-13. Sec., Dr. Robert C. Cochrane, Room 37, State House, Boston.

MICHIGAN:* *Examination.* Ann Arbor and Detroit, June 11-13. Sec., Dr. E. C. Swanson, 118 Stevens T. Mason Bldg., Lansing.

MINNESOTA:* *Examination and Reciprocity.* Minneapolis, June 12-14. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Examination.* Jackson, June 25-26. *Reciprocity.* Jackson, June 27. Asst. Sec., Dr. R. N. Whitfield, Old Capitol, Jackson.

MISSOURI: *Examination.* St. Louis, May 30-31 and June 4-5. Exec. Sec., Mr. John A. Hailey, State Capitol Bldg., Box 4, Jefferson City.

MONTANA: *Examination and Reciprocity.* Helena, Oct. 2-3. Sec., Dr. S. A. Cooney, 7 West 6th Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 18-20. Director, Bureau of Examining Boards, Mr. Husted K. Watson, 1009 State Capitol Bldg., Lincoln.

NEVADA: *Examination.* Carson City, July 4-5. *Reciprocity.* Reno, July 3. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

NEW HAMPSHIRE: *Examination and Reciprocity.* Concord, Sept. 12-13. Sec., Dr. John S. Wheeler, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, June 19-22. Sec., Dr. Patrick H. Corrigan, 28 W. State St., Trenton.

NEW MEXICO:* *Examination and Endorsement.* Santa Fe, May 21-22. Sec., Dr. R. C. Derbyshire, 227 E. Palace Ave., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York City and Syracuse, June 26-29. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany.

NORTH CAROLINA: *Examination.* Raleigh, June 18-21. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 11-13. *Reciprocity and Endorsement.* Grand Forks, July 14. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* Columbus, June 14-16. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OKLAHOMA:* *Examination.* Oklahoma City, June 5-6. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON:* *Examination.* Portland, July 16-17. Ex. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 9-12. Acting Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Examination.* Providence, July 5-6. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 25-26. Sec., Mr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Custer, July 17-19. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TENNESSEE:* *Examination.* Nashville, June 7-8 and Memphis, June 13-14. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 18-20. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 11-13. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VERMONT: *Examination.* Burlington, June 13-15. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Reciprocity.* Richmond, June 13. *Examination.* Richmond, June 14-16. Address, Board of Medical Examiners, 631 First St., S.W., Roanoke.

WASHINGTON:* *Endorsement.* Seattle, July 15. *Examination.* Seattle, July 16-18. Sec., Mr. Edward C. Dohm, Olympia.

WEST VIRGINIA: *Examination.* Charleston, July 16-18. *Reciprocity.* Charleston, July 20. Sec., Dr. N. H. Dyer, State Office Bldg. No. 3, Charleston.

WISCONSIN:* *Reciprocity.* Madison, Spring; *Reciprocity and Examination.* Milwaukee, July 10-12. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, June 4. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage, Fairbanks, Juneau and other towns. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

HAWAII: *Examination.* Honolulu, July 9-10. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

VIRGIN ISLANDS: *Examination and Endorsement.* Charlotte Amalie, June 13-14. Sec., Dr. Earle M. Rice, St. Thomas.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: *Examination and Reciprocity.* Tucson, June 19. Sec., Mr. Herbert D. Rhodes, University of Arizona, Tucson.

CONNECTICUT: *Examination.* New Haven, June 9. Address: State Board of Healing Arts, 258 Bradley St., New Haven 10.

DISTRICT OF COLUMBIA: *Examination.* Washington, Oct. 22-23. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., N.W., Washington.

FLORIDA: *Examination.* Miami, June 9. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

IOWA: *Examination.* Des Moines, July 10. Sec., Dr. Ben H. Peterson, Coe College, Cedar Rapids.

MINNESOTA: *Examination.* Minneapolis, June 5-6. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis 14.

NEVADA: *Examination.* Reno, July 3. Sec., Dr. Donald S. Cooney, Box 9005, University of Nevada, Reno.

NEW MEXICO: *Examination and Endorsement.* Santa Fe, July 15. Sec., Mrs. Marguerite Cantrell, Box 1522, Santa Fe.

OKLAHOMA: *Examination and Reciprocity.* Oklahoma City, Sept. 28-29. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON: *Examination.* Portland, June 2, Sept. 8 and Dec. 1. Dr. Earl M. Pallett, Sec., State Board of Higher Education, Eugene.

RHODE ISLAND: *Examination.* Providence, Aug. 29. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH DAKOTA: *Examination.* Vermillion, June 8-9. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: *Examination.* Memphis, July 2-3. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis 3.

TEXAS: *Examination.* Austin, October. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WASHINGTON: *Reciprocity.* Seattle, July 10. *Examination.* Seattle, July 11-12. Sec., Mr. Edward C. Dohm, Olympia.

WISCONSIN: *Examination.* Milwaukee, June 2. Final date for filing application was Mar. 30. Madison, Sept. 21. Final date for filing application is Sept. 13. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

ALASKA: *Examination and Reciprocity.* Anchorage and Juneau, first week of February, April, June, August and November. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

*Basic Science Certificate required.

DEATHS

Knapp, Arnold, New York City; born in New York City Aug. 20, 1869; College of Physicians and Surgeons, medical department of Columbia College, New York City, 1892; professor of ophthalmology at his alma mater, now known as the Columbia University College of Physicians and Surgeons, from 1903 to 1928, when he became professor emeritus; specialist certified by the American Board of Ophthalmology; in 1931 president of the American Ophthalmological Society which in 1937 bestowed on him its Lucien Howe medal for meritorious mendation of the Association for Research in Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology; the Leslie Dana Gold medal, given on recommendation of the Association for Research in Ophthalmology and awarded annually by the St. Louis Society for the Blind through Lester Dana of St. Louis for achievements in the prevention of blindness and the conservation of vision, was presented to him in 1941; in 1946 became the second American to deliver the Bowman Lecture before the Ophthalmological Society of the United Kingdom and was elected to honorary membership; honor member of the Société Française d'Ophthalmologie and of the Deutsche Ophthalmologische Gesellschaft; executive surgeon at the Herman Knapp Memorial Eye Hospital until it merged in 1940 with the Institute of Ophthalmology of the Columbia-Presbyterian Medical Center and until his retirement in 1950 served as consultant at the latter institute; a director of the Knapp Foundation in Ophthalmology at Columbia University; an associate member of the American Medical Association and chairman of its Section on Ophthalmology, 1925-1926; formerly consultant at Presbyterian, Roosevelt, and the Harlem Eye and Ear hospitals; in 1953, on the occasion of the 25th anniversary of the founding of the Columbia Presbyterian Medical Center, received a Distinguished Service award; author of "Medical Ophthalmology," published in 1917; assumed editorship of *Archives of Ophthalmology* in 1911, a position he held for 38 years; Columbia University awarded him the honorary degree of doctor of science in recognition of his outstanding achievements; died in Harkness Pavilion, Columbia Presbyterian Medical Center, Feb. 29, aged 86, of arteriosclerotic heart disease.

Babcock, Carvelle, Jackson, Miss.; University of Chicago, The School of Medicine, 1953; interned at the Research and Educational Hospitals in Chicago and the Doctors Hospital in Washington, D. C.; served a residency at the Barnes Hospital in St. Louis; a resident in pathology at the University of Mississippi Medical Center; died March 19, aged 29.

Baldwin, Arthur Fletcher ⊕ Waterloo, N. Y.; University of Michigan Medical School, Ann Arbor, 1930; health officer of Waterloo; on the staff of the Memorial Hospital; died in the Clifton Springs (N. Y.) Sanitarium and Clinic March 30, aged 56, of coronary infarction.

Bennett, Frederick Robert ⊕ Chicago; Rush Medical College, Chicago, 1929; member of the American Academy of General Practice; died April 12, aged 53, of hypernephroma.

Boyles, Herman Davidson, New Castle, Pa.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1909; died Feb. 28, aged 76, of arteriosclerotic heart disease.

Campbell, Ephraim E. ⊕ Butler, Pa.; Medico-Chirurgical College of Philadelphia, 1906; served during World War I; died March 7, aged 79.

Collins, James Alexander, Gordonville, Texas; Memphis (Tenn.) Hospital Medical College, 1904; on the staff of the Wilson N. Jones Hospital in Sherman, where he died March 1, aged 76, of encephalopathy due to arteriosclerosis.

Curtis, Morris Williams ⊕ Reading, Pa.; Jefferson Medical College of Philadelphia, 1932; served during World War II; died in the Reading Hospital Feb. 29, aged 50, of coronary occlusion.

⊕ Indicates Member of the American Medical Association.

Dawson, Drexel Lowry ⊕ Milwaukee; University of Illinois College of Medicine, Chicago, 1913; fellow of the American College of Surgeons; served during World Wars I and II; on the staff of the Veterans Administration; died March 2, aged 67, of cancer.

Deane, Herbert C., Salt Lake City; Denver College of Medicine, 1894; died March 9, aged 83, of myocarditis.

de Bono, Manoel ⊕ Amityville, N. Y.; University of Malta Faculty of Medicine and Surgery, Valletta, Malta, 1922; served during World War II; died Jan. 7, aged 59, of coronary thrombosis.

Elliott, Gilbert David, Jeffersonville, Ohio; Medical College of Ohio, Cincinnati, 1896; died March 5, aged 86, of coronary heart disease.

Fields, Robert Burroughs ⊕ La Porte City, Iowa; Rush Medical College, Chicago, 1903; died in the Halifax Hospital, Daytona Beach, Fla., March 7, aged 81, of cerebral vascular accident.

Foster, Ralph Kelsey ⊕ Columbia, S. C.; Medical College of the State of South Carolina, Charleston, 1909; served during World War I; for many years associated with the Veterans Administration; died Feb. 2, aged 71, of arteriosclerosis and heart disease.

Gaw, Lois Boyd, Sanford, N. C.; Woman's Medical College of Baltimore, 1907; died in the Lee County Hospital Feb. 6, aged 78, of subarachnoid hemorrhage, hypertensive cardiovascular disease, and arteriosclerosis.

Jackson, William Long ⊕ Burlington, Wash.; Jefferson Medical College of Philadelphia, 1910; served during World War I; county health officer; died March 3, aged 75, of a heart attack.

Leavitt, Henry Hooker ⊕ Minneapolis; Chicago Homeopathic Medical College, 1886; fellow of the American College of Surgeons; at one time professor of ophthalmology at the University of Minnesota College of Homeopathic Medicine and Surgery; died in the Franklin Hospital March 18, aged 94, of pneumonia.

Miller, Irving Cleveland ⊕ Berlin, Pa.; Medico-Chirurgical College of Philadelphia, 1914; died in the Meyersdale (Pa.) Hospital Jan. 17, aged 71, of carcinoma of the right lung.

Moorhead, Arthur Clyde ⊕ New York City; Chicago Homeopathic Medical College, 1902; served during World War I; died March 2, aged 80.

Pogue, George L. Alphonso, Bedford, Va.; Leonard Medical School, Raleigh, N. C., 1911; died in Roanoke March 6, aged 67.

Schuchardt, Irvin Peter Lawrence, Aberdeen, S. D.; Rush Medical College, Chicago, 1936; member of the South Dakota State Medical Association; served during World War II; on the staff of St. Luke's Hospital, where he died Feb. 6, aged 49, of coronary thrombosis.

Seaberg, Simon Peter ⊕ Spokane, Wash.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1906; died March 26, aged 77, of coronary thrombosis.

Sullivan, John Thomas, Sr. ⊕ Chicago; Chicago College of Medicine and Surgery, 1914; died April 15, aged 77, of cerebral thrombosis.

Waltrip, Powhatan Merle, Jr. ⊕ Fort Worth, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1927; served during World War II; died in the U. S. A. F. Hospital, Carswell Air Force Base, Dec. 30, aged 53, of cirrhosis of the liver.

Wilson, Clarence Benjamin, New York City; Howard University College of Medicine, Washington, D. C., 1951; served an internship and residency at Morrisania City Hospital number 52; died in Mexico Jan. 20, aged 35.

FOREIGN LETTERS

AUSTRIA

Distribution of Hydrocortisone.—At the meeting of the Society for Internal Medicine in Vienna on Feb. 9, Dr. G. Geyer reported the results of a clinical-experimental study showing that intravenously injected hydrocortisone flows from the blood vessels into the tissues. The steroid diffuses within the first 50 minutes after the injection and then reaches an equilibrium between the plasma and extravascular space of distribution, with an intravascular remainder of less than 10% of the total amount of the drug injected. Further studies indicate that hydrocortisone is stored in the fibroblasts.

The Vectorcardiogram.—At the same meeting, Dr. K. Hupka stated that the diagnosis of myocardial infarction in a patient who also has a block in the conductive nerves of the heart, and particularly in its left branch, can be made with the aid of the electrocardiogram. The vectorcardiogram has proved to be a diagnostic adjunct in such patients. The vectorcardiographic tracing in patients with interventricular heart block and myocardial infarction undergoes characteristic changes and frequently shows bizarre abnormalities.

Influence of Adrenal Cortical Extract.—At the meeting of the Society for Internal Medicine in Vienna on March 8, Dr. H. Frischauf stated that administration of a lipid adrenal cortical extract for five days caused a moderate but not persistent retention of sodium. Potassium diuresis, which was observed temporarily, did not persist when the administration of the hormone was continued. The serum values of sodium, potassium, and chlorine remained unchanged. A slight drop of the urinary pH and an increase in titratable acidity was traced to an increased absorption of alkali. A change in acid-base equilibrium could not be demonstrated, and the same applied to changes in extra or intracellular fluids but an increase of 2 lb. (0.9 kg.) in body weight in one week was observed with a high-salt diet. Blood pressure did not increase in the course of the treatment. Comparison of the effects of various adrenal cortical hormones makes a predominance of the effect of aldosterone likely, if one considers the reported doses of the hormones.

Blood Ammonium Level in Hepatic Disease.—At the same meeting, Dr. N. Stefenelli stated that in hepatitis there is no characteristic level of ammonium in the blood and that most of the time it is normal. In cirrhosis of the liver, it is usually increased and normal values occur only exceptionally. In some comatose patients with cirrhosis, a parallelism can be demonstrated between cerebral manifestations and the increased ammonium level. The ammonium level in the blood was determined according to Conway's method. The term ammonium also includes compounds of the blood that, soon after the blood sample has been taken, liberate ammonium.

Metabolism of Iron Saccharate.—At the same meeting, Drs. Gisinger and Vetter stated that, after the intravenous injection of ferrisaccharate tagged with radioactive iron in subjects, the ferrisaccharate rapidly disappeared from the blood and was absorbed by the reticuloendothelial cells of the liver and probably of the spleen. There the complex was split up and, within 20 minutes after the injection, the Fe^{59} reappeared in the blood, but this time in the ionized form. The radioactive iron then passed into the erythrocytes through the bone marrow and in the iron depots respectively.

COLOMBIA

Seminar on Medical Education.—The first Seminar on Medical Education was held at the Universidad del Valle in Cali in December. The purposes of the seminar were (1) to obtain information on the progress and standards of teaching; (2) to discuss the curriculum and methods of teaching now in use; (3) to make recommendations for improving medical education; and (4) to establish closer relations and scientific interchange between the various schools of medicine. In the immediate past, theoretical aspects have predominated over practical methods with too little laboratory work; there have been too few full-time professors for the number of students enrolled; there has been no determination of the progress made by the students; absenteeism and unreliability among teachers have been marked because appointments have been political; changes in curriculum and medical directors have been frequent; and the budgets have been insufficient to meet minimal needs. The only private school of medicine in Colombia spends the smallest amount of money per student per annum. The needs of the universities are well known but steps to remedy the conditions are always postponed. It is hoped that better results will grow out of the recent seminar.

FINLAND

BCG Vaccination.—BCG vaccination was first adopted in Finland in 1941, but since then there has been a steadily growing appreciation of its value. By the end of 1947 a total of 170,000 persons had been vaccinated. Mass BCG vaccination was undertaken in 1948 when 743,000 of Finland's total population of just over 4 million inhabitants were tested with tuberculin and 325,000 were vaccinated with BCG. Of these 93,000 were between the ages of 15 and 25 years. In 1949, 184,000 persons were vaccinated, and since then the annual number of vaccinations with BCG has been about 130,000. This vaccination has been compulsory for some time for probational nurses, medical students, and the staff of tuberculosis hospitals, and since the beginning of 1954 it has been so for everyone reaching the age of 19 years. In other respects it is voluntary.

TURKEY

Effect of Petroleum Benzin on Intestinal Parasites.—In the *Bulletin of Istanbul University Medical Faculty* (vol. 14, no. 2), Tavat and Bial reported on the use of pure petroleum benzin as a polyvalent anthelmintic. Of 104 patients treated with this agent, 70 were given ambulant treatment. Because of gastrointestinal or other conditions, 34 patients were admitted to the hospital. Eighty-seven patients were infested with a single type of parasite, and 17 patients had two to four kinds. The petroleum benzin used was free from benzol, lead salts, and aromatic hydrocarbons. The emulsion consisted of one part of petroleum benzin, one of syrup of acacia, one and a half of water, and a few drops of menthone. Adults were given 25 to 50 cc. of the emulsion on an empty stomach, followed by a purgative two hours later. The patients were encouraged to drink water copiously. A light breakfast was allowed two hours after defecation. Several patients had nausea and mild vertigo, but severe toxic side-effects were not observed. Of the total series, 88 patients expelled the parasites. In 8 of the remaining 16, the treatment was repeated and in 4 of these it was successful. Especially good results were obtained in four patients infested with Necator americanus. Several of the 59 patients infested with Taenia saginata and other parasites had previously taken anthelmintics several times without success. In 49 of the 59 patients, the therapy was effective. In patients infested with taeniae and ascarides, the therapy became effective after seven to eight hours. Most patients infested with Trichuris and Oxyuris organisms expelled both parasites. Patients with the latter were given the benzin emulsion by mouth and by enema. In the patients who were observed for three to five months, the stools remained negative. One patient infested with Hymenolepis nana failed to expel the parasite although the treatment was given several times.

UNITED KINGDOM

Diet and Anemia.—At a symposium held in March by the Nutrition Society, the chairman, Sir Stanley Davidson, said that in Britain anemia in women of child-bearing age is still common, although not so severe as it used to be. Megaloblastic anemia is more common because the patients with it are treated and do not die from the disease as they used to. The textbook picture of pernicious anemia is now rarely seen. Professor Platt of London said that much anemia is due to protein deficiency. The first effect of protein deprivation is not a fall in the protein content of the muscle or blood, but a marked fall in the level of circulating hemoglobin. In infections the hemoglobin level falls. Platt attributes this to a toxic destruction of protein, which manifests itself as increased nitrogen excretion. Professor Woodruff of London said that the hospitals of India are filled with anemic child-bearing women. In one town 13.4% of maternal deaths are due to anemia. The two commonest causes of tropical anemia are hookworm and protein malnutrition. Biopsy of livers of pregnant women in Nigeria showed hepatic enlargement, fibrosis, and fatty infiltration, which is probably due to protein deficiency. The anemia of these patients does not respond to iron until the serum proteins are raised; hypoproteinemia impairs the synthesis of hemoglobin.

Dr. F. Wokes of King's Langley reported on a sect of 700 vegetarians who eat no animal food whatsoever. Their protein intake is only about 10 to 12 gm. daily. Although the hematogram is not like that of pernicious anemia, they do suffer from subacute combined degeneration of the spinal cord, which was the cause of death of two patients. This form of anemia is attributed to insufficient intake of vitamin B_{12}, which has been confirmed by blood studies. These people have a high intake of folic acid and a low intake of vitamin B_{12}—a combination that favors subacute combined degeneration in the patient with pernicious anemia. Dr. C. C. Ungley said that vitamin B_{12} deficiency can produce central scotomas.

Dr. J. R. Evans of London described studies with vitamin B_{12} labeled with radioactive cobalt. The absorption of the vitamin can be calculated from the intake and output, which are determined from the radioactivity of the cobalt. In patients with pernicious anemia, only 10% of a dose of vitamin B_{12} is absorbed, the normal figure being 50 to 75%. Absorption is increased if intrinsic factor is administered. Patients who have had a total gastrectomy show diminished absorption because the mucosa-forming intrinsic factor has been removed. With partial gastrectomy this area is retained. Patients with idiopathic steatorrhea and intestinal infections also showed diminished absorption of vitamin B_{12}. It is doubtful if the vitamin B_{12} formed in the intestines by bacterial action is available because, if the intestinal wall is sterilized, the amount of the vitamin absorbed is unchanged.

Nystatin, an Antimycotic Antibiotic.—Nystatin (Mycostatin) is an antibiotic prepared from Streptomyces noursei with an inhibitory action on the growth and cell division of Candida albicans and some species of Saccharomyces. Stewart has used it to treat mycotic infection occurring as a complication of oral antibiotic therapy (*Brit. M. J.* 1:658, 1956). Twenty-two patients with fungal hyphae demonstrable in direct examination of films made from sputum and cultures positive for C. albicans were treated with three or four daily oral doses of 500,000 units of nystatin for several days. In these patients moniliasis had developed as a complication of therapy with various antibiotics and was characterized by copious greyish sputum containing epithelial fragments colonized by C. albicans. Rapid and complete clearance of infection occurred in 16 patients and temporary clearance occurred in 4. Apart from transient nausea, no toxic effects were observed. Strains of Candida were reisolated from 20 patients during or after courses of nystatin, but they showed no change in degree of sensitivity to the drug in vitro. Nystatin was also applied topically to pharyngeal monilial lesions with good results; swabs were negative and the lesions subsided in a few days. When nystatin was given prophylactically, it was not wholly successful in preventing mycotic superinfection in patients receiving antibiotics by mouth. Resistance to nystatin was not found in strains after passage in vitro or on reisolation during and after treatment.

Childs (*Brit. M. J.* 1:660, 1956) reported a series of 50 men with pneumonia, who had not been given adequate chemotherapy before admission. Alternate patients were given 0.25 gm. of tetracycline every six hours or tetracycline with 500,000 units of nystatin every eight hours. On admission and before treatment rectal and throat swabs were taken and a specimen of sputum obtained from each patient. These were repeated on the third, fifth, seventh, and ninth days. Swabs and sputum were examined and cultivated for C. albicans and yeasts. The nystatin was effective in reducing the growth of Candida in the intestine, but not in the throat and sputum. It would appear from this trial that when given by mouth nystatin did not appear in the blood stream in adequate concentration to produce sufficient systemic effect.

Damp and Rheumatism.—The Scientific Coordinating Committee of the Empire Rheumatism Council has objected to the court ruling whereby a Glasgow teacher was recently awarded $5,600 against her employer, the Glasgow Corporation, because she was alleged to have developed rheumatoid arthritis through working in damp and unhealthy conditions. The committee, which considers that this case raises serious issues, states that in a country such as Great Britain, where most people are subjected to cold and damp, strong evidence is needed before etiological significance can be attributed to these factors. While cold and damp may cause symptomatic aggravation, evidence that they cause rheumatoid arthritis is lacking. This confusion between symptomatic aggravation and causation of disease is still extremely common and is not confined to the lay mind.

Medical Degrees at Oxford.—In the future physicians will be able to qualify at Oxford with the bachelor of medicine degree without first obtaining the Oxford degree of bachelor of arts, which has always been required in the past. This decision is the outcome of the development of the clinical school at Oxford, which began during the war. Formerly the Oxford medical student obtained a baccalaureate degree after four years and then proceeded to do his hospital work in London, returning to receive his final medical degree at Oxford three years later. At present some remain in Oxford doing their clinical studies at the Radcliffe Infirmary. In the future, provided they have completed three years' study in the medical sciences and have obtained a baccalaureate degree in science, students from other universities can proceed directly to the final Oxford medical degree of bachelor of medicine without first receiving the bachelor of arts degree. In this way it is hoped to attract good students from other universities in Great Britain and overseas.

Nasal Carriers of Micrococcus Pyogenes.—Brodie and his coworkers carried out a six months' serial survey for carriers of Micrococcus pyogenes in a group of 30 student nurses from the start of their training in the nursing school to their work in the wards (*Brit. M. J.* 1:667, 1956). The prevalence of antibiotic-resistant strains of coagulase-positive micrococci was ascertained and the serologic types studied. This study was prompted by the observation that outbreaks of micrococcic infection are relatively infrequent in hospitals, although the nurses often have a high carrier rate. Examination of the nasal micrococci of each nurse was made at weekly intervals while the student nurses spent three months in the preliminary training school of a general hospital away from the patients and the subsequent three months in the wards. It was discovered that cross infection of nasal micrococci to the nurses takes place after they have taken up their duties in the wards and that the frequency of isolation of coagulase-positive micrococci also increases during this period. While the evidence points to the nurse as a potential source of infection, observations indicated that she becomes infected during her duties in the ward. Failure to demonstrate cross infection of micrococci during preliminary training away from the wards, when the nurses live in a semiclosed community, suggests that infection is picked up at some point in the handling of the patients during nursing. The survey demonstrated that the micrococci responsible for hospital infections consist of a relatively small number of types. The extent of micrococcic cross infection in a hospital can be assessed from examination of the nasal micrococci in the nursing staff.

CORRESPONDENCE

EPIDEMICS OF MICROCOCCIC INFECTIONS IN INFANTS

To the Editor:—In a recent epidemic of micrococcic (staphylococcic) infections in the nurseries for newborn infants at the Ohio State University Hospital, a single strain of Micrococcus pyogenes, phage type 42B/47C/44A/52, was found to be responsible for all lesions. A report of this epidemic is to be published in *Pediatrics.* Since that time we have had opportunities to study organisms responsible for similar epidemics among newborn infants and nursing mothers in Portsmouth and Lancaster, Ohio; Lepeer, Mich.; Seattle; Hartford, Wis.; and Philadelphia and have found that in every instance phage type 42B/47C/44A/52 was responsible. This suggests that epidemics of this sort in nurseries for newborn infants may be a disease entity caused by a single strain of M. pyogenes. In all but one instance the strains from the various epidemics mentioned above also demonstrated an identical pattern of antibiotic sensitivity. Studies of this problem are being continued by the departments of pediatrics and bacteriology at Ohio State University. We would appreciate receiving cultures from pustular lesions of infants or purulent breast lesions of mothers obtained during nursery outbreaks of epidemic proportions. Reports of bacteriological findings will be promptly transmitted. Cultures and communications should be addressed to the Phage Typing Laboratory, Department of Bacteriology, Ohio State University, Columbus 10, Ohio.

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ANTICOAGULANT THERAPY

To the Editor:—The Norwegian correspondent writing in the Foreign Letters section (*J. A. M. A.* **160:**583 [Feb. 18] 1956) has misinterpreted three important points regarding my article on anticoagulant therapy (*Nord. med.* **54:**1733 [Nov. 17] 1955). Firstly, he states: "In order to achieve a specific quantitative test for both prothrombin and proconvertin, he [Owren] has combined the Russell viper venom method for determining prothrombin with use of proconvertin-free ox plasma (or congenitally proconvertin-free human plasma) as a reagent." This statement is incorrect. The prothrombin-proconvertin method was developed as an entirely new method to measure the combined effect of prothrombin and proconvertin in a single test. It is specific for neither factor and bears no direct relationship to either the viper venom method for prothrombin or the specific proconvertin method. Indeed, in describing the viper venom method for prothrombin (*J. Lab. & Clin. Med.* **46:**89 [July] 1955), the statement is made that "neither this nor any other method which measures prothrombin alone should be used to control anticoagulant therapy with Dicumarol or similar drugs." Secondly, the correspondent states: "Control tests three times a week have usually been found sufficient," whereas I stated that these are usually necessary only once every three weeks. Finally, the statement that mortality in cases of angina pectoris "compares well" with the series from the Mayo Clinic is misleading. The Mayo series shows an over-all mortality of about 9% after the first year, as compared to 5% for my series.

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PERSONAL HEALTH RECORDS

To the Editor:—About a year ago I devised a folder called "Health Notes." It is a simple, brief, and yet effective method for recording details regarding disease and accidents, and it could be a partial answer to Dr. Carl A. Dragstedt's plea for a personal health log as set forth in his guest editorial in THE JOURNAL, April 14, 1956, page 1320. It is common knowledge that the practicing physician can find no patient who knows, in accurate detail, his own medical history, much less that of his family, and this fact constitutes a serious defect in applying good medical care. It is surprising that every medical student is taught, at great length, how to elicit the chief complaint, the present illness, and the history, but no instruction is given to the medical student about how he might help his patients keep such a record in the first place.

When a new mother reports to the office for her six-weeks' postpartum examination, I give her this folder for the record of her newborn infant. I fill in the items under "birth data," then she keeps the facts about immunizations as they are carried out. The next category is headed "diseases and accidents of childhood," then "family history" and "diseases and accidents of adulthood," with a final place for notes on annual physical examinations. These "Health Notes" have proved so popular that the mother will often ask for extra copies for each of the children at home. I have also started to give these to the young women who come in for premarital examinations, because just before they leave home they can accumulate details of health importance from the parents and often the grandparents. The "Health Notes" are printed on high-grade rag paper, and the folder is encased in a cellophane envelope for two reasons: first, to protect it and keep it clean, and, second, because the visibility of the title would prevent discarding it accidently with other papers. This method was reported to the American Academy of Obstetrics and Gynecology in Chicago in December, 1955.

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MISUSE OF DIURETICS

To the Editor:—There is a flagrant misuse of acetazolamide (Diamox) and mercury. We know that serious consequences may occur after the use of both in persons with cardiac disease. However, no mention has been made of the routine misuse of acetazolamide or mercurial diuretics in heart failure. When patients have diabetes we never routinely place them on insulin therapy without testing the urine sugar level. Yet most clinicians and internists will not hesitate to prescribe daily use of acetazolamide or weekly injections of mercury in cases of cardiac failure without finding out whether the patient who is edematous has or has not a low urine salt level. If a patient has hypochloremia or hypochloruria he definitely may be seriously hurt by these remedies. Persons with edema must be studied for salt in the blood and urine before prescribing medication to correct edema. Patients who administer to themselves any of these remedies should check their urine for salt. How many so-called cardiac deaths may actually be due to low-salt syndromes?

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MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Cardiovascular Diseases Treated with a Total Extract of Heart Muscle—a Clinical Contribution. A. Grigolato, A. Merli and V. Noseda. Minerva med. 47:178-182 (Jan. 24) 1956 (In Italian) [Turin, Italy].

A total extract of heart muscle (Ricosen) was given to patients suffering from the anginal syndrome. There was a complete disappearance of the attacks or a decrease in their intensity and frequency. Ricosen has both a direct and an indirect dilating effect on the coronary arteries, and it regulates the metabolism of the myocardial fibers. In patients with congestive heart failure Ricosen, when given together with cardiotonics, increases the action of digitalis, helps it to be better utilized, and reduces or neutralizes its toxic effect. Treatment with Ricosen is more useful if given at intervals between one cycle of therapy with digitalis and another. The extract does not have a hypotensive effect. It is beneficial when used in patients with hypertension. The benefit is due to the action of Ricosen on the coronary circulation and on the regulation of the metabolism of the myocardial fibers.

BCG and Vole Bacillus Vaccine in the Prevention of Tuberculosis in Adolescents: First (Progress) Report to the Medical Research Council by Their Tuberculosis Vaccine Clinical Trials Committee. P. D'A. Hart, J. Charles, R. Cruickshank and others. Brit. M. J. 1:413-427 (Feb. 25) 1956 [London, England].

The early results of a controlled clinical test of BCG and Mycobacterium muris (vole bacillus) vaccines in the prevention of tuberculosis in adolescent boys and girls now under way in Great Britain show that the degree of protection against tuberculosis conferred by both these vaccines is substantial. The general plan of the trial was to include more than 50,000 boys and girls who were in their final year at secondary modern schools in or near North London, Birmingham, and Manchester and who were almost all between the ages of 14½ and 15 years; participation in the test was to be voluntary and the participants were to have the written consent of their parents. More than 56,700 children had been included by December, 1952. Those giving a negative reaction to tuberculin were divided by an effectively random process into three groups: those in one group were not vaccinated, those in another received BCG vaccine, and those in the third received Myco. muris vaccine. Children who reacted positively to 3 tuberculin units formed one group and those who reacted positively to 100 tuberculin units formed another; both were left unvaccinated. Participants in each of the five groups have been followed intensively by means of a 14-month cycle of inquiry and examination, each cycle consisting of a postal inquiry, a home visit by a health visitor, and an examination including a chest radiograph and tuberculin tests. Contact was made with 94% of the participants by at least one of these three means within 18 months of entry, and information has since been obtained from many of the remaining 6%.

All definite and suspected cases of tuberculosis discovered by these methods or by information obtained from medical health officers or chest clinic records were reviewed and classified by an independent assessor unaware both of the results of all the tuberculin tests and of whether any vaccination had been performed. Definite cases beginning within 2½ years of entry to the trial numbered 165. Pulmonary tuberculosis was present in 63% and pleural effusion without evidence of pulmonary tuberculosis in 22%; in 68% the condition was severe enough to require discontinuance of work for at least three months. No deaths were caused by the disease within the two and one-half-year period. The annual incidence of tuberculosis in the tuberculin-negative unvaccinated group was 1.94 per 1,000; in the BCG-vaccinated group it was only 0.37 per 1,000; and in the Myco. muris-vaccinated group it was only 0.44 per 1,000. Each vaccine therefore conferred a substantial and similar degree of protection against tuberculosis over a two-and-one-half-year period in adolescence. Supplementary incomplete information suggests that this protection, which becomes evident soon after the vaccination, is maintained up to four years. Complications of vaccination consisted of occasional regional adenitis and delayed healing of the local lesion. Two cases of erythema nodosum were also attributed to BCG vaccine; in addition, lesions indistinguishable from lupus vulgaris apppeared in a number of the children who were given Myco. muris vaccine. Entrants with a positive reaction to 3 tuberculin units had an annual incidence of tuberculosis of 1.75 per 1,000 as compared with 0.74 per 1,000 in those positive only to 100 tuberculin units. Those whose reactions to 3 tuberculin units were strong (indurations of 15 mm. or more) had an incidence of 2.93 per 1,000 as compared with 0.78 per 1,000 among those with indurations of from 5 to 14 mm. The risk of developing tuberculosis thus seems to be especially high in children in this age group who are highly sensitive to tuberculin. These findings will be supplemented by further information as the study progresses.

Antituberculous Activity of Antirabic Vaccine. G. Angela. Arch. sc. med. 81:60-64 (Jan.) 1956 (In Italian) [Turin, Italy].

The results of studies made on guinea pigs to evaluate the usefulness of antirabic vaccine in the treatment of tuberculous infections are reported. Two groups of animals were inoculated with Mycobacterium tuberculosis. The animals of one group served as controls, and those of the other were treated with Fermi-Semple vaccine. In an attempt to determine whether the vaccine had a specific action, a third group of guinea pigs was inoculated and then treated with a brain emulsion of healthy rabbits. All the animals that were treated received the treatment for from 25 to 30 days, some starting on the day of the inoculation, others 20 days thereafter. After this time they were killed and autopsy was performed.

It was found that the administration of antirabic vaccine induces a pronounced involution of the tuberculous lesions that are already present and markedly retards the progression of those that are caused by the concurrent inoculation with Myco. tuberculosis. This effect does not seem to be due to a stimulating nonspecific action of the brain substance in which the vaccine is incorporated; although the general condition was definitely better in the guinea pigs that had been treated only with the brain emulsion of healthy rabbits, the tuberculous lesions were notably severe and extensive. The hypothesis is advanced that the inactivated rabies virus, present in the vaccine, produced in the organism of the guinea pigs an immunity reaction that interfered with the development of the Myco. tuberculosis. Studies are in progress to establish the nature of this reaction, namely, whether it is a nonspecific reaction in the sense that it may have effect also against other infections and whether the immunity can be passively carried from the immune to the ill animal. The possibility that there may be a synergistic action between the virus and the brain substance with regard to the immunity reaction is also being investigated.

The place of publication of the periodicals appears in brackets preceding each abstract.

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Cortisone and Tuberculosis of the Lungs. G. Poggio, G. Lingiardi and A. Wrubl. Minerva med. **47**:212-218 (Jan. 27) 1956 (In Italian) [Turin, Italy].

The authors studied the effect of cortisone on 78 patients with tuberculosis of the lungs. The hormone, if administered in small quantities and for a short period of time, may increase the therapeutic effect of the antibiotics. In cases of recent exudative disease where the person is young and has not undergone too much treatment with antibiotics, cortisone proves to be very efficacious. Cortisone is not so effective, and may prove harmful, in chronic processes that have already shown a resistance to antibiotics. In older patients in particular, cortisone can cause hypofunction of the adrenal glands. The authors do not believe that cortisone increases the process of deterioration of the lung tissue affected with tuberculosis. Cortisone does not work contrary to the beneficial effects of antibiotics. The effect of cortisone lasts as long as it is administered. The benefit depends on the patient's age, the stage of the disease, and the ability of the body to react to antibiotics.

The Leptomeningeal Hemorrhagic Syndrome. A. Pendini. Minerva med. **47**:172-178 (Jan. 24) 1956 (In Italian) [Turin, Italy].

The author discusses the leptomeningeal hemorrhagic syndrome from the clinical and etiological points of view. The clinical course depends upon the degree of hemorrhage. If it is not massive, it is accompanied by mental haziness but never by loss of consciousness. The oculomotor nerves are usually affected, mainly the third, fourth, and sixth. In leptomeningeal hemorrhage the blood is always mixed with the cerebrospinal fluid; there is no coagulation, and after sedimentation the cerebrospinal fluid just above the erythrocytes becomes xanthochromatic. Twelve clinical cases are described, and the pathogenic aspects of the disease are considered according to Noferi's scheme: leptomeningeal hemorrhage in hemorrhagic syndrome and leptomeningeal hemorrhage in acquired diseases.

Retroclavicular Block Dissection in the Diagnosis of Sarcoidosis of the Lung. B. Carstensen, A. Odelberg and F. Wahlgren. Lancet **1**:265-266 (Feb. 11) 1956 [London, England].

Three hundred cases of pulmonary sarcoidosis were detected at a sanatorium in Sweden during the past five years. Since the unequivocal diagnosis of sarcoidosis of the lung is practically impossible, the authors have adopted the following criteria: 1. The patient should have the typical history and signs and/or radiographic evidence. The relative paucity of symptoms contrasts with the widespread extent of the lesions. Hyperglobulinemia should be sought. 2. Other diseases (e. g., tuberculosis, pneumonoconiosis, Hodgkin's disease, neoplasm, and the mycoses) should be excluded. 3. Corroborative histological evidence should be obtained by biopsy of lymph nodes and by Kveim's test. The authors found retroclavicular block dissection invaluable and have applied this method in 304 patients since the beginning of 1952.

After injection of a local anesthetic, the skin and platysma muscle are incised for 3 to 4 cm. parallel with, and 1 to 2 fingerbreadths above, the clavicle. The superficial fascia is incised along the lateral border of the sternocleidomastoid muscle, which is retracted medially, exposing the pad of fat on the anterior surface of the scalenus anterior muscle. Care should be taken to avoid injuring the lymphatic duct on the right side and the phrenic nerve and the thoracic duct on the left side. Sometimes the omohyoid muscle lies rather low, in which case the pad of fat is grasped above that muscle. The pad is drawn forward and examined. Lymph nodes (which are part of the mediastinal system) may be visible or palpable, and these are removed; but if no node is detected, as much as possible of the pad is removed. The incision is then closed. In sarcoidosis the lymph nodes are diffusely and often densely infiltrated by discrete, usually spherical, epithelioid cell clusters of roughly uniform size. Some of these clusters contain giant cells of the Langhans type in which inclusion bodies are occasionally found. Sarcoidosis should never be diagnosed on the basis of the histological findings alone. Biopsy by this method supported the diagnosis in 148 (62%) of 237 patients with clinical and radiographic evidence of sarcoidosis.

SURGERY

The Beck Operations for Coronary Heart Disease: An Evaluation of 63 Patients Selected for Operation. H. Feil, W. H. Pritchard, H. K. Hellerstein and others. Ann. Int. Med. **44**:271-283 (Feb.) 1956 [Lancaster, Pa.].

This report is concerned with 63 patients in whom Beck operations for coronary heart disease were performed. The Beck 1 operation consists of abrasion of the epicardium and lining of parietal pericardium, application of an inflammatory agent (0.2 gm. of powdered asbestos) to these surfaces, partial occlusion of the coronary sinus where it enters the right auricle, and grafting of parietal pericardium and mediastinal fat to the surface of the heart. The Beck 2 operation of arterialization of the coronary sinus consists of two stages and occasionally of three. In the first stage a vein graft is placed between the aorta and the coronary sinus, providing a direct communication between these vessels. Stage two is the narrowing of the coronary sinus to 2 to 3 mm. two or three weeks later. This latter procedure provides an escape channel for the arterialized blood, which passes from the aorta to the coronary sinus if the pressure in the coronary sinus becomes excessive. This safety valve prevents over-engorgement of the myocardium. Stage three (performed in five patients) consists of complete ligation of the coronary sinus at a later date.

The Beck 1 operation was done in eight patients in whom for various reasons it was impossible to place the vein graft. The Beck 2 procedure was chosen as the more suitable operation in 55 patients in the present series. Forty-nine of these had a direct aorta-coronary sinus anastomosis or a venous graft communication. Six patients who were selected for the Beck 2 operation could not have the aorta-sinus graft placed. The reasons for this failure included, among others, heart stoppage while the pericardium was opened, supraventricular tachycardia, ventricular fibrillation, shock during anesthesia, and death during the operation.

There were no deaths among the eight patients who underwent the Beck 1 operation. The operative mortality in the Beck 2 operation was approximately 25%. The operation, in addition to its production of intercoronary vessels, actually adds a burden to the heart and circulation by increasing cardiac output and blood volume. In a few instances there was increase in blood pressure and in heart rate. In some patients, cardiac failure was induced and the coronary sinus had to be ligated. This operation, then, in its present state of development, should be held in abeyance. The Beck 1 operation, while still an experimental procedure, may be reserved for patients who are invalided by pain not relieved by medical therapy. Improvement from any therapy depends on the remaining intact musculature's receiving an augmented blood supply. The data in this small series do not permit any conclusions.

Auricular Thrombosis and Embolism in Mitral Stenosis. A. Actis-Dato, A. Tarquini and P. F. Angelino. Minerva med. **47**: 24-30 (Jan. 6) 1956 (In Italian) [Turin, Italy].

Five hundred patients with mitral stenosis in whom a mitral valvotomy was performed were studied to determine the frequency with which thrombi are found in the auricle during the operation and the eventual relationship that exists between this finding and the presence of emboli before, during, and after the intervention and between the auricular thrombosis and the cardiac rhythm. The preoperative diagnosis of the presence of thrombi in the auricle is extremely difficult, if not impossible. A tentative diagnosis can be made on the basis of a history of previous embolism. Thrombosis was found in the left auricle of 56 of the 500 patients (11.2%). In seven instances the thrombus was of recent formation. Auricular thrombosis was found most often in the patients who were older than 30 years. It was present in 20.1% of the men and only 6.9% of the women studied. Auric-

ular fibrillation played an important role in the causation of the auricular thrombosis. This was found in 47 (35.3%) of the 133 patients who had auricular fibrillation, whereas it was found in only 9 (2.4%) of the 367 patients who had sinus arrhythmia. The greater the dilatation of the left atrium, the greater, other conditions being equal, the probability of the presence of auricular thrombosis. There seemed to be a certain relationship between the degree of the stenosis and the presence of the auricular thrombosis in the sense that the latter was found most often in patients in whom the valve orifice was most involved by the stenosis. Embolism had occurred preoperatively in one-fourth of the patients with auricular thrombosis, whereas it occurred during or after the operation in about one-fifth of them. The operative and immediate postoperative mortality was significantly greater among the patients in whom auricular thrombosis was found. Of the 17 patients who died, 9 had auricular thrombosis.

Modifications Induced by Mitral Commissurotomy on Functional Activity of Kidney. A. Amerio, A. Vercellone, P. P. Gaido and others. Minerva med. **47**:1-6 (Jan. 6) 1956 (In Italian) [Turin, Italy].

The glomerular and tubular function and the circulatory dynamics of the kidney were studied in 23 patients with mitral stenosis a few days before and 30 days after mitral valvotomy. As a rule, the kidney of patients with mitral stenosis is characterized by a vascular dysfunction that is shown by a frequent and often marked deficit of blood flow to the organ. The glomerular activity is altered only slightly and the tubular function is good. The results of this comparative study indicated that one month after the valvotomy the functional aspect that was altered preoperatively had been restored to normal. The functional capacity of the glomerular filtering surface had not been markedly altered, and the concentrating capacity of the kidney had not been disturbed in any way by the intervention. Although hemodynamic factors of an ischemic nature play a great part in conditioning the peculiar circulatory status of the kidney of patients with heart disease, the degree of stenosis of the orifice and the consequent reduction in the systolic output are also determining factors. The improvement that was observed in the kidney function of these patients 30 days after the valvotomy is thus explained.

Parietal Pleurectomy for Recurrent Spontaneous Pneumothorax. E. D. Gaensler. Surg. Gynec. & Obst. **102**:293-308 (March) 1956 [Chicago].

Gaensler reviews the accepted treatments for spontaneous pneumothorax and its complications. Exploratory thoracotomy and local wedge or segmental excision of the offending lesion appear to be the treatments of choice for recurrent spontaneous pneumothorax. He describes a new technique for the treatment of recurrent spontaneous pneumothorax for patients in whom local excision is not applicable either because resection of all the blebs would entail loss of an unjustifiably large amount of functioning lung tissue or because no lesions can be found on the lung surface. The new technique consists of parietal pleurectomy. Continued mobility and unimpaired functioning of the thoracic cage after dissection of the parietal pleura have been demonstrated. Two criteria are regarded as indications for parietal pleurectomy: a documented history of two or more episodes of spontaneous pneumothorax on the same side and thoracoscopic or operative evidence of extensive pleural involvement by blebs or vesicles. During 1954, seven patients who met these criteria were treated. Additional pleurectomies were performed when two of these patients returned after repeated episodes of pneumothorax on the opposite side. All were young men and all had had at least two or as many as five episodes of pneumothorax on the same side. Complications were minimal after nine total or subtotal parietal pleurectomies. Objective studies of ventilatory function and bronchospirometry revealed no measurable loss of pulmonary function. Attempts at postoperative induction of artificial pneumothorax proved unsuccessful, and there have been no recurrences of spontaneous pneumothorax on the side operated upon. Parietal pleurectomy may also be applicable in patients with recurrent or chronic pneumothorax who prove to have no detectable abnormality of the lung surface or show multiple cracks or leaks of the visceral pleura without associated blebs. Pleurectomy is preferred over chemically or mechanically induced pleuritis because it entails fewer complications and shortens hospitalization and because the potential pleural space and thus the chance of recurrence are eliminated.

An Evaluation of the Surgical Treatment of Carcinoma of the Stomach. J. B. Beal and M. R. Hill Jr. Surg. Gynec. & Obst. **102**:271-278 (March) 1956 [Chicago].

The surgical treatment of carcinoma of the stomach at the New York Hospital from 1932 to 1954 was reviewed. Fifty-two of a total of 557 patients were not subjected to operation; in these the diagnosis was established by biopsy of distant metastases or at autopsy. Surgery was limited to exploration and biopsy in 151 patients, and palliative procedures were carried out in 97 patients. Removal of the carcinoma with the intent to accomplish cure was carried out in 257 patients, of whom 33 died during or immediately after the operation. Partial resection was done in 219 patients, of whom 190 underwent distal resection, with 25 surgical deaths (13.2%), and 29 had proximal resections (esophagogastrectomy), with 3 surgical deaths (10.3%). Total gastrectomy was done in 38 patients, with 5 deaths (13.2%).

Of 133 patients surviving subtotal gastric resection before 1949, 44 or 33.1% survived for five or more years. Of the 12 having a successful total gastrectomy before 1949, 3 or 25% survived five years. Of 17 who underwent esophagogastrectomy before 1949, 3 or 17.6% survived five years. Local recurrence of carcinoma in the upper gastrointestinal tract was demonstrated in 30 of the 224 patients who survived removal of the gastric neoplasm with curative intent. Twenty-five of these occurred after partial gastrectomy, four after esophagogastrectomy, and one after total resection of the stomach. The recurrence after total gastrectomy was detected in the esophagus, and the recurrence after other procedures was found in the gastric remnant in each instance. Since in the past considerable emphasis has been placed on the occurrence of malnutrition after removal of the entire stomach but little attention has been paid to the occurrence of such disturbances after partial resections, the authors investigated this and found that nearly one-half of the patients who had been subjected to partial gastrectomy had definite digestive disturbances. They feel that the efficacy of total gastrectomy cannot be adequately assessed on the basis of available information. In view of the decreasing operative mortality and better understanding of the management of gastrointestinal sequelae, a more extensive trial of total gastrectomy should be undertaken in the treatment of more favorable lesions.

NEUROLOGY & PSYCHIATRY

Evaluation of Combined Coramine-Electroshock Therapy in the Treatment of Schizophrenia. P. W. K. Ligthart, R. P. Johnston and E. Sussman. Am. J. Psychiat. **112**:619-623 (Feb.) 1956 [Baltimore].

The studies described were carried out to determine whether the results of standard electroshock therapy could be improved by the use of Coramine (the diethylamide of pyridine-3-carboxylic acid). Thirteen female patients with schizophrenia (consecutive new admissions) were given electroshock therapy in conjunction with administration of 5 cc. of Coramine injected intravenously. The next 13 consecutive female schizophrenic patients admitted were given 5 cc. of sodium chloride solution intravenously in conjunction with their electroshock therapy. These patients were graded with the Wechsler-Bellevue intelligence scale and the Bender-Gestalt test just prior to their electroshock series and were retested five weeks after their last treatment.

Results indicate that Coramine, used in conjunction with electroshock therapy, significantly decreased the time spent in electroshock therapy. Patients receiving Coramine returned to a higher level of intellectual functioning and to a more adequate perception of reality than did the controls. It is assumed that Coramine-electroshock therapy brings about an increased blood

flow and that thalamic stimulation occurs, so that most of the effects are similar but greater than after standard electroshock therapy. The addition of Coramine obviates the need for "intensive electroshock therapy" in excited patients and thus avoids the confusion resulting from such treatment. Patients treated with electroshock plus Coramine experience less fear and appear more receptive to psychotherapy. Acutely ill newly admitted patients benefit most. This is a pilot study, and the results should be considered tentative. A two-year follow-up of these patients would be necessary to draw any definite conclusions as to the permanency of the effects of Coramine-electroshock therapy.

Sudden Death After Electric Shock Treatment Due to Tracheal and Bronchial Obstruction. W. Tuteur. Am. J. Psychiat. **112:**624-626 (Feb.) 1956 [Baltimore].

While most fatalities caused by electroshock are caused by pathological changes in the cardiovascular system, the author describes a fatality that was probably caused by obstruction of the trachea and bronchi, since, while the heart and brain were completely intact at autopsy, there was congestion of the trachea and main bronchi with viscous pus-like mucous material. The patient had been in restraint and as a result was unable to ventilate his air passages properly and thus had accumulated a large amount of viscous secretion in his airways. During electroshock treatment the secretion may have reached the narrower lower bronchi and increased his dyspnea. Artificial respiration may have had, in this case, an adverse effect, because the secretion may have been pumped farther down and probably caused a complete obstruction. Care should be taken to have a patient ventilate properly before electric shock treatment, especially after he has been in continuous restraint for a considerable length of time.

Value of Newer Tissue Culture Methods in Epidemiological Inquiries: An Illustrative Outbreak of Poliomyelitis. A. J. Beale, M. W. Fujiwara, W. Stackiw and others. Canad. M. A. J. **74:** 337-342 (March 1) 1956 [Toronto, Canada].

The discovery by Enders and others that poliomyelitis virus can be isolated in tissue cultures has greatly improved epidemiological studies on poliomyelitis. The authors describe a poliomyelitis outbreak that occurred in April, 1955, in Toronto. The new tissue-culture methods, particularly monkey-kidney cultures, were used as an adjunct to the conventional methods of epidemiological inquiry. The outbreak is of interest because it appeared to be initiated by a 41-year-old man who had returned from Mexico on April 2, feeling unwell and with mild diarrhea. He became ill again on April 11, with fever, drowsiness, headache, and vomiting. Difficulty in swallowing developed the next day, and on April 13 he was admitted to hospital. Later, he developed weakness of his shoulders. His youngest daughter, aged 3 years, also fell ill on April 11 with similar symptoms and was admitted to hospital on April 13. She later developed a lower motor neurone facial palsy. Nonparalytic poliomyelitis also developed in a 9-year-old child of this family, but two other children, aged 7 and 4, remained healthy. Poliomyelitis also developed in two children of a neighboring family, in a school contact of one of these, and in a neighbor of this last child. Routine quarantine measures were taken against the families of the poliomyelitis patients, and no additional cases occurred.

Stools were obtained from the seven patients, and all yielded type 1 poliomyelitis virus in tissue culture. In addition, type 1 poliomyelitis virus was isolated from the two healthy children (aged 7 and 4 years) of the first family. The usefulness of the tissue-culture method in confirming the clinical diagnosis of poliomyelitis is once again demonstrated. The first two cases were not typical clinically at the outset, and, in view of the rarity of poliomyelitis in Toronto as early in the year as April, the laboratory confirmation of the diagnosis was valuable. The authors believe that, with trypsinized monkey-kidney cultures, virus can be isolated in nearly every case of clinically typical paralytic poliomyelitis. Four of the six patients from whom two-phase serum samples were obtained showed a fourfold or greater rise in antibody titer, which would be sufficient to establish the diagnosis even in the absence of virus isolation. Two patients had as high a titer in the acute as in the convalescent sample, so that the serologic results alone did not establish a diagnosis of recent poliomyelitis infection. The occurrence of such antibody patterns illustrates that virus isolation is a more sensitive method of diagnosis and is of course much faster.

GYNECOLOGY & OBSTETRICS

Determination of the Genetic Sex with the Aid of Vaginal Smears. P. J. Carpentier, L. A. M. Stolte and G. P. Visschers. Nederl. tijdschr. geneesk. **100:**154-157 (Jan. 21) 1956 (In Dutch) [Haarlem, Netherlands).

The determination of the genetic sex by finding the so-called sex chromatin in the epithelial nuclei of skin biopsy specimens has received much attention in clinical studies on patients with hermaphroditism and in patients with ovarian agenesis. The authors observed that the sex chromatin could be recognized quite clearly in the exfoliated pavement-epithelium cells of vaginal smears that had been stained according to Papanicolaou's technique. They reasoned that this should be possible in other smears such as in those of the oral or the urethral mucosa. They were able to verify this in studies on mucosal smears of men and women, but in comparing the oral and vaginal smears of the same person, they found that the latter were generally more suitable for the determination of the genetic sex than smears from the oral mucosa. Vaginal smear preparations were available from 49 patients with primary amenorrhea. Examination of these smears led to the discovery of ten genetic males, and in three of these cases it was possible to verify the diagnosis of ovarian agenesis syndrome. This syndrome is more frequent in genetic males.

Influence of Pregnancy and Lactation on the Incidence of Mammary Carcinoma Induced with Methylcholanthrene in Female Mice of the "IF" Strain. J. Marchant. J. Path. & Bact. **70:**415-418 (Oct.) 1955 [Edinburgh, Scotland].

Many strains of mice have a high natural incidence of mammary cancer that is partly due to the presence of a factor transmitted from one generation to the next in the mother's milk. In some of these strains the mammary tumor incidence has been found to be higher among breeding females than it is among virgins, indicating that hormonal stimulation also has an influence on their development. Other strains of mice, free from the milk factor, have a low incidence of spontaneous mammary cancer, but it is generally possible to induce mammary tumors in these strains with the aid of carcinogenic hydrocarbons. Breeding females show a higher incidence than nonparous females, and mammary tumors can sometimes be induced in male mice treated with estrogens. The Bonser IF strain is one of the strains of mice with a low natural incidence of mammary cancer, but this strain is particularly sensitive to carcinogenic hydrocarbons.

In studying the influence of breeding in this strain of mice on the incidence of tumors induced with carcinogenic hydrocarbons, the author found that a high incidence of mammary tumors (75%) was induced with methylcholanthrene in virgin mice of the IF strain. No tumors were induced in naturally breeding mice that were allowed to lactate before methylcholanthrene treatment began, and the incidence was 29% when treatment began before breeding. These results indicate that lactation has a significant effect in lowering the incidence of induced mammary tumors in IF mice. The protective effect of lactation in this strain makes it worthy of further study in view of the fact that it parallels the situation in women.

PEDIATRICS

Prophylaxis in the Eyes of Newborn Infants: A Comparison of Silver Nitrate and Erythromycin. H. E. Wachter and M. M. Pennoyer. Missouri Med. **53:**187-190 (March) 1956 [St. Louis].

Of 12,599 babies born between March, 1953, and May 31, 1954, in five hospitals in St. Louis, 5,489 were given treatment for the prevention of gonorrheal conjunctivitis in the newborn by the introduction of 1% silver nitrate solution into each conjunctival sac, while in 7,110 infants a ½-in. strip of erythromycin

ophthalmic ointment was placed as the prophylactic agent in the conjunctival sac of each eye without subsequent irrigation. Records of the number and severity of conjunctival reactions were kept in 2,333 infants, 1,071 of whom received 1% silver nitrate and 1,262 of whom received erythromycin ointment. Reactions were graded daily as to their severity, and three grades were distinguished, i. e., redness and swelling (grade 1), redness, swelling, and discharge (grade 2), and redness, swelling, and purulent discharge (grade 3). Grade 1 reactions were two and one-half times more frequent with silver nitrate than with erythromycin, grade 2 reactions were 5 times more frequent with silver nitrate than with the antibiotic ointment, and grade 3 reactions were produced 13 times more frequently with silver nitrate than with erythromycin. All observers were impressed with the superiority of the antibiotic to silver nitrate in its lower incidence of irritation. No case of gonorrheal conjunctivitis was observed among the 12,599 infants. Erythromycin ophthalmic ointment was found to be easy to apply, stable for long periods without refrigeration, and at least as effective as silver nitrate in the protection of the eyes of newborn infants against gonococcic infection.

Acute Hematogenous Osteomyelitis. M. Green, W. L. Nyhan and M. D. Fousek. Pediatrics **17**:368-382 (March) 1956 [Springfield, Ill.].

The clinical records of 99 infants and children under 15 years of age admitted to the Grace–New Haven Community Hospital with acute hematogenous osteomyelitis during a 31-year period have been reviewed in relation to the symptomatology, early clinical findings, and response to therapy. Some of the patients presented chiefly local manifestations attributable to the infection in the bone; in others, the onset suggested a systemic septic illness. All but three of the patients had fever either before or after admission. Pain or tenderness was present on admission in 80 patients. Localized tenderness is a highly significant but by no means common finding; it was present on admission in 17 patients only. Limitation of joint movement, evident in 53 cases, was sometimes the only initial finding in infants. Joint movement of any kind was impossible in some instances, and at times the reduction in movement even suggested paralysis. Swelling was found in 84 patients on admission, but was the initial symptom in only one. Fluctuation, which indicates rupture of the periosteum, is a comparatively late sign; it was present on admission in 18 patients.

The early differentiation of osteomyelitis from rheumatic fever may be extremely difficult, especially when carditis is absent. Septicemia without localization; septic arthritis, which may occur as a coexistent process; and cellulitis also present difficult problems in differential diagnosis. Less frequent possibilities requiring exclusion include poliomyelitis, neoplasms, fractures and traumatic injuries, leukemia, thrombophlebitis, transient synovitis of the hip, and osteitis pubis. Involvement of the bony pelvis was unusually frequent in these patients; otherwise, the femur, the tibia, and the humerus were the bones most often affected. Antecedent illness or trauma that might have established a predisposition to osteomyelitis or favored its localization occurred in 70% of the patients. A specific bacterial diagnosis was made in 87% of the cases; in 63% the causative organism was a Micrococcus (Staphylococcus). A beta-hemolytic Streptococcus was regarded as responsible in 18 cases. Positive roentgenographic signs of osteomyelitis appeared in 89% of the children from 3 to 17 days after the onset of symptoms (average, 10 days). The mortality and morbidity decreased progressively until in the period from 1949 to 1954 there were no deaths and only two patients had a hospital stay of 50 days or more. Therapeutic emphasis during the first 15 years was on early incision and drainage; after the advent of penicillin, it was found that early and vigorous treatment with antibiotics would obviate the need for surgical intervention in many cases. Chloramphenicol and erythromycin may be used at first in combination with penicillin or streptomycin; later, when the infecting organism has been identified, the regimen may be changed if necessary. Immobilization and supportive therapy should not be neglected. Treatment in patients with suspected osteomyelitis should be continued for at least three weeks after onset; if at the end of that period the roentgenograms are still normal and clinical signs and symptoms have been absent for a week, it can probably be discontinued with safety. Patients with proved osteomyelitis, however, will require longer treatment: at least two weeks should elapse after all local signs of inflammation have subsided and the temperature and leukocyte count have returned to normal before the treatment is discontinued.

Familial Dysautonomia: Pulmonary Manifestations. R. E. Moloshok and J. E. Moseley. Pediatrics **17**:327-333 (March) 1956 [Springfield, Ill.].

The nature of the pulmonary manifestations of familial autonomic dysfunction has been studied in the light of significant pulmonary difficulties observed in 13 of 20 children with this syndrome. Repeated episodes of pneumonia or bronchitis necessitating hospitalization were the presenting complaints of 9 of the patients; in all 13 the respiratory symptoms began during infancy. Fever, cough, and dyspnea usually characterized the episodes of respiratory difficulty. The physical signs were either those associated with diffuse or localized bronchopneumonia or those found in asthmatic bronchitis. Diffuse moist rales and wheezes in the chest appeared suddenly in several patients in connection with eating or emotional upsets. Bronchial hypersecretion with secondary obstruction of the bronchi seems to be primarily responsible for the pulmonary manifestations evident in children presenting this syndrome. Pulmonary emphysema or atelectasis follows varying degrees of bronchial obstruction, and secondary infection may supervene. Pneumonia or some other pulmonary infection was often suspected in these patients, especially when fever and respiratory symptoms appeared together. Pathogenic organisms, however, were isolated in only a few instances, and the response to treatment with numerous antibiotics and chemotherapeutic agents was unsatisfactory. Bronchial hypersecretion and pulmonary edema have been produced experimentally by central nervous system injury, and in these patients autonomic dysfunction, rather than infection, appears to have been the chief cause of the fever and pulmonary manifestations. Bronchoscopy, performed at least once in each of six patients, revealed in most instances only clear mucoid secretions in the bronchi.

The varying combinations of infiltration, atelectasis, and emphysema found in the roentgenograms are practically indistinguishable from those of fibrocystic disease of the pancreas, and six of the children were extensively investigated with this condition in mind. The similarity of the findings in the two conditions is probably due to the fact that both are characterized by bronchial obstruction and tenacious viscid secretions. Recognition of the nature of the respiratory difficulties found in patients with familial autonomic dysfunction and familiarity with the roentgenographic appearance of the chest in this disorder may lead to its early identification and the establishment of a correct diagnosis.

Hemophilic Hemarthrosis in Early Childhood and Its Treatment. G. B. Benedetti and R. Lamura. Minerva pediat. **7**:1613-1624 (Dec. 15) 1955 (In Italian) [Turin, Italy].

Hemarthrosis is a severe and extremely common complication of hemophilia. Generally, it appears when the patient is 4 to 5 years old as a consequence of trauma. It can involve any joint, but involvement of the knee joint is observed most frequently (85% of cases). Hemophilic hemarthrosis is a joint effusion the duration of which varies according to the anatomic and functional characteristics of the joint that is involved. In 15% of cases of hemophilic hemarthrosis of the knee joint the effusion lasts from two to three months, whereas in 85% it progresses slowly to a stage of panarthritis. So far, the treatment of this complication has given poor results.

The authors suggest a therapeutic scheme that has given them good results in six cases. It consists of (1) emergency treatment of the hemarthrosis and (2) prophylactic treatment of the relapses. The former aims at restoring to normal the general blood condition of the patient by means of transfusions of plasma or blood given every two or three days. The local treatment at this time is limited to immobilization of the joint. Then

when the altered coagulation time has been brought to normal or almost normal (generally this occurs two hours after a transfusion) the joint is punctured to remove the fluid; it is washed with lukewarm sodium chloride solution; thrombin (which is diluted at the time it is used) is injected into the joint; and a pressure bandage is applied. The second part of the therapeutic scheme consists in continuing the transfusions two or three times weekly for at least two months, depending on the patient's blood coagulation time, while the joint is kept in a plaster cast at absolute rest for 15 days. After this time, active and passive movement can be started. Weight should not be placed on the joint before one month has elapsed from the time the hemarthrosis occurred. With this therapeutic regimen, the eventual onset of those inflammatory and degenerative episodes that lead to panarthritis and subsequently to ankylosing arthrosis is prevented. The histories of the six patients in whom this therapeutic scheme was used are described.

Investigations on the Predisposition to and Prognosis of Postvaccinal Encephalitis. A. Herrlich, W. Ehrengut and J. Weber. München, med. Wchnschr. **98:**156-159 (Feb. 3) 1956 (In German) [Munich, Germany].

A total of 78 cases of postvaccinal encephalitis occurred in Bavaria in the years between 1940 and 1955. In the course of catamnestic studies, the families of 55 of these patients were visited. A search was made for endogenic and exogenic factors that might produce a predisposition for postvaccinal encephalitis. There was evidence that age was a factor. Female infants seemed particularly vulnerable, but this factor requires further clarification. The prognosis of the disease is doubtful. More than half of the 78 patients died. A large number of the survivors developed sequelae (57%). Individual patients may have a predisposition for a postvaccinal encephalitis, but predisposition does not seem the decisive factor in the onset of the disease in all cases.

UROLOGY

"Granulomatous Orchitis." H. J. Spjut and J. D. Thorpe. Am. J. Clin. Path. **26:**136-145 (Feb.) 1956 [Baltimore].

A clinically and pathologically unusual and apparently little-known lesion, "granulomatous orchitis" (an orchitis with a granuloma-like pattern), is presented and discussed. The authors found 12 such lesions in a group of orchiectomy and biopsy specimens. Three had been diagnosed pathologically as granulomatous orchitis, one as Hodgkin's disease, one as a tumor, and the rest as chronic orchitis. Clinically, nine had been recorded as inflammatory processes and three as tumors. Microscopically, the granuloma-like lesions had the seminiferous tubules as their foundation and appeared to originate in or from these. The lesions were within the testes in 11 cases and confined to the rete testis in one. In no case was the granulomatous change complete; a few recognizable seminiferous tubules remained. There was evidence to indicate that Sertoli cells are the precursors of the epithelioid cells in the transition from normal to the granulomatous pattern. In most cases the stroma between the lesions showed increased numbers of collagen fibers and infiltration, principally with leukocytes, lymphocytes, and plasma cells. Seven cases of acute orchitis were also studied, but a transition from acute to granulomatous orchitis could not be clearly shown. The pathogenesis of orchitis with granuloma-like pattern is not known, but it does appear that trauma is a predisposing factor. Eight of the authors' 12 patients had a history of trauma. Spermatozoa or products of their degeneration extravasated because of trauma or perhaps acute inflammation may cause the granuloma-like reaction in the testis and epididymis. In this study, it was shown from slide preparations of acute orchitis that spermatozoa do escape from necrotic seminiferous tubules into the interstitial tissue. However, the granuloma-like lesions of granulomatous orchitis seem to be confined to the tubules, which suggests that either the disease does not pass through an acute necrotizing phase or the extravasated spermatozoa do not stimulate granuloma formation in the interstitial tissue. This is not necessarily true for the epididymis, where the granulomatous lesions are of a different histological character and location.

Prostatic Serum Acid Phosphatase in Patients with Localized Prostatic Cancer. J. H. Hill. Am. J. Clin. Path. **26:**120-130 (Feb.) 1956 [Baltimore].

A study was undertaken to determine whether a significant number of patients with primary carcinoma limited to the prostatic gland have abnormally elevated prostatic serum acid phosphatase levels that could be used for diagnosis of the disease in its curable stages. Three groups of patients were examined: group 1 consisted of 44 patients with prostatic cancer, in 21 of whom the disease was localized to the area of the prostate gland and had not been treated; group 2 was made up of 118 patients with benign prostatic disease; and group 3 comprised 285 men with various diseases not involving the prostate. Phosphatase activity of serum was determined by the King-Armstrong method, in which disodium phenyl phosphate is the substrate, and by a second method in which the substrate is paranitrophenyl phosphate. Most of the serum samples were tested by both methods. The mean total and prostatic serum acid phosphatase levels were essentially the same in group 3 as in group 2, while group 1 as a unit had mean total and prostatic values significantly higher than the other two groups. The 17 patients with treated localized cancer had about the same values as the patients of groups 2 and 3, but, as expected, the 2 out of 6 patients with demonstrable metastases who had not been treated had very high levels of total and prostatic serum acid phosphatase. Unfortunately, in spite of the definitely increased mean values for both serums in patients with localized untreated disease, the incidence of elevated values was low. It would seem that determination of the prostatic serum acid phosphatase level is a more accurate diagnostic aid than determination of the total serum acid phosphatase level, since more of the patients with prostatic cancer of all types showed an increase in the former than in the latter. However, this superiority was not conclusively demonstrated in the patients with localized untreated prostatic cancer under the conditions described.

Contribution to Treatment of Carcinoma of the Prostate with Diethylstilbestrol Diphosphate (Honvan). W. Fular. Medizinische, No. 8, pp. 285-288 (Feb. 25) 1956 (In German) [Stuttgart, Germany].

A 68-year-old man was admitted to the surgical department of the Julius Hospital in Würzburg, Germany, for an ileus-like condition. Roentgenologic examination revealed a tumor in the left lower region of the abdomen that appeared to be in the prostate and that caused bilateral compression of the urinary passages. The poor general condition and the erythrocyte sedimentation rate suggested a malignancy. Palpation revealed typical carcinoma of the prostate. Roentgenograms of the vertebral column showed definite metastases. There were suspicious shadows in the pelvis. Phosphatase determination also suggested a metastasizing carcinoma of the prostate. The carcinoma originated in the prostate, and cystoscopy revealed small, tuberous, lateral lobes. The neoplasm extended predominantly subvesically in the left half of the pelvis and caused a partial intestinal obstruction. Pressure on the left pelvic veins caused edema of the patient's left leg.

The patient was given intravenous injections of 2 ampuls (500 mg.) of diethylstilbestrol diphosphate (Honvan) daily for six days, 1 ampul (250 mg.) daily for 17 days, and then 250 mg. every second day. After one month of treatment the size of the tumor was reduced by more than half. The patient's subjective condition was improved, and he was discharged on his request, but injections of the drug were repeated at home, three times weekly. The patient was readmitted to the hospital nine months later because of severe back pain. The general condition was poor, although the tumor could no longer be demonstrated. Phosphatase determinations showed considerable deterioration. Five hundred milligrams of diethylstilbestrol was administered

daily for 16 days, 250 mg. for the following 12 days, and then again 500 mg. daily for one month. The patient's condition improved considerably, and he was discharged. Roentgenograms showed definite spotty decalcification.

The patient was admitted to the hospital seven months later because of a sudden deterioration of his condition. Death resulted from heart failure. In addition to the metastasizing carcinoma of the prostate, the patient had extensive thrombosis of the aorta, infarcts of the myocardium, brain, spleen and kidneys, and embolism in a branch of the mesenteric artery and in the right femoral artery. The prostate was not increased on macroscopic examination. Nodular diffuse deposits were found in the entire vertebral column. A uniformly hyalinized indurated mass with sparse connective-tissue nuclei and embedded sclerotic vessels was found in the prostatic tumor and in the nodes. Xanthomatous cells and lymphocyte and plasma-cell infiltrates were observed in circumscribed areas. There was no trace of the carcinoma. The diethylstilbestrol diphosphate therapy had transformed the clinically established carcinoma of the prostate into a hyalinized indurated mass.

Diabetic Pneumaturia. R. D. Foord, J. D. N. Nabarro and E. W. Riches. Brit. M. J. **1**:433-434 (Feb. 25) 1956 [London, England].

Primary pneumaturia, that is, pneumaturia occurring in the absence of instrumentation or a bladder fistula, though rare, is more common in patients with diabetes than in nondiabetic persons. It is associated with infection of the urinary tract, and the gas, which is odorless and consists largely of hydrogen, is formed by the action of the infecting organisms, usually Escherichia coli, on the glucose in the urine. The possibility of diabetes in patients with pneumaturia cannot be excluded merely by testing the urine for sugar because the sugar may be completely removed from the urine by the action of the bacteria, so that the result of the test is negative. Blood sugar estimations must therefore be made or the urine must be tested after the infection has been controlled. Evidence of obstruction in the lower urinary tract, or residual urine as a result of diabetic neuropathy or a vesical diverticulum, can be found in most of the patients with pneumaturia.

Treatment directed toward the control of glycosuria by suitable diabetic management and the elimination of infection by antibiotics or chemotherapy, combined in one case with relief of obstruction of the urinary tract, led to the disappearance of pneumaturia in two patients recently seen by the authors. One of these, an obese woman aged 67 who had had diabetes for 20 years, required small daily doses of sulfonamides to keep the urine sterile and insure the absence of symptoms. The second patient, an obese 63-year-old man known to have glycosuria, was eventually found to have a urethral obstruction due to enlargement of the prostate. A retropubic prostatectomy was performed, and three months later he was symptom-free. Tests showed the urine to be free from sugar, though still infected. He has since remained well on a low-calorie, low-carbohydrate acid-ash diet.

Effect of Temperature, Humidity and Dehydration on Formation of Renal Calculi. C. L. Prince, P. L. Scardino and C. T. Wolan. J. Urol. **75**:209-215 (Feb.) 1956 [Baltimore].

A series of 922 consecutive cases of acute renal colic caused by ureterolithiasis showed that there is a definite seasonal incidence of this disease. The incidence of acute ureterolithiasis follows to a remarkable degree the average mean temperature; the greatest number of cases were observed from April to October and the fewest in February. The authors feel that the high temperatures existing in the first period mentioned in their part of the country (Savannah, Ga.) result in dehydration, urinary concentration, and increased stone formation. If patients can be induced to take large quantities of fluid, particularly in the hot months, the number of cases of acute ureterolithiasis can be reduced. Recurrence of stones was rare in the present series, presumably because the patients heeded the admonition to take more fluids after their experience with renal colic and stone passage or removal. Relative humidity apparently had no definite influence on the incidence of acute ureterolithiasis.

OPHTHALMOLOGY

A New Type of APC Virus From Follicular Conjunctivitis. E. Jawetz, L. Hanna, S. J. Kimura and P. Thygeson. Am. J. Ophth. **41**:231-234 (Feb.) 1956 [Chicago].

The adenoidal-pharyngeal-conjunctival (APC) viruses constitute a group that can be subdivided into serologic types by means of specific neutralization tests. The authors briefly mention earlier reports on eight different serologic types and point out that to date APC virus type 6 has not been encountered in clinical illness, and has been isolated only once from adenoid tissue in tissue culture. They describe observations on two patients with eye infection in which APC virus type 6 was isolated and in which the patients demonstrated by their specific antibody response that it was the etiological agent of their illness.

The first patient, a 26-year-old physician, complained of conjunctivitis with a "foreign-body sensation" in the left eye. There was a "pea-sized" left preauricular lymph node but no discharge from the eye. There was marked tearing and congestion of tarsal and bulbar conjunctiva with intense follicular hypertrophy in the lower fornix. Scrapings taken from the conjunctiva were inoculated into twice-washed HeLa cell cultures, and a maintenance medium of 10% chick serum in mixture 199 was added. After five days of stationary incubation at 36 C, cytopathogenic effects were noted; cell degeneration was almost complete by the seventh day. The type of degeneration was compatible with the type seen with APC viruses. The virus was typed by neutralization test and shown to belong to type 6 of the APC group. The inflammation of the eye did not change materially for several days, and then the conjunctivitis subsided gradually, leaving no residuum except for conjunctival edema persisting for two weeks. Symptoms of systemic illness, with temperature of 101 F (38.3 C), muscle pains and aches, and moderate prostration appeared a week after the onset of the eye symptoms and lasted about two days. This patient, who was an intern, had examined many persons with "red eye" at a San Francisco hospital.

The second patient, also a physician, had a sensation of scratchiness in both eyes with mild scleral injection. Accompanying this, he had an "annoying sensation of fullness in the tissues surrounding the pharynx." Approximately one week prior to onset, his wife had had an identical illness, and their four children, ranging in age from four months to five years, had had very similar illnesses. Type 6 APC virus was isolated from the right eye of the physician on the second day of illness. The virus isolated from the first of these two physicians was employed in a serologic survey of persons aged 9 to 44 years living in California. Twelve of 36 serums (33%) obtained between 1952 and 1955 had neutralizing antibodies to type 6 APC virus in a dilution of 1:10 or greater. Huebner and others had found that the incidence of neutralizing antibodies against APC type 6 in the general population of Washington, D. C., was about 30%. Thus, there is serologic evidence in at least two separate regions of the United States (Eastern Seabord and California) that one-third of the population may acquire infections with APC virus type 6 before the age of 45 years.

The Changes in the Fundus of the Eye in Arterial Hypertension. H. Elwyn. A. M. A. Arch. Ophth. **55**:1-8 (Jan.) 1956 [Chicago].

Changes in the fundus of the eye in hypertension present two distinct pictures. One is due to slowly progressive changes in the retinal arteries as the result of aging and of arteriosclerosis but there is no abnormal contraction of the retinal arteries. The second picture is due to an abnormal contraction of the retinal arteries with secondary changes in the substance of the retina, and constitutes arteriospastic retinopathy. The first picture is the one seen throughout the benign phase of essential hypertension. Aging of arteries is characterized by (1) a lessening of the elasticity of the vessel walls, with the artery becoming longer and wider, and (2) a diffuse thickening of the intima. These changes occur to a moderate degree in old people, but are exaggerated in cases of long-standing hypertension. The lessening of the elasticity is shown by the tortuosity of the retinal arteries and by the widening of the light reflex. A hiding of a portion of the vein on

each side of the artery that crosses it, irregularities in the course of the arteries, and occasionally arteries that have a copper-wire or a silver-wire appearance are other details of the fundus in benign essential hypertension.

The second picture, that of arteriospastic retinopathy, especially as seen in young persons, is not due to chronic progressive changes in the wall of the arteries but rather to a sudden contraction or narrowing of most or all of the retinal arteries. As a result of this narrowing of the arteries, the terminal vessels, the capillaries, dilate, producing hyperemia. This peristatic hyperemia is seen on the optic disk, which is redder than usual; tiny vessels are sometimes seen. Later the capillary wall permits erythrocytes to pass through, with the formation of hemorrhages. In some arterioles the contraction has narrowed the lumen to such a degree that tiny infarcts are produced, which ophthalmoscopically give the appearance of cotton-wool patches. When the narrowing of the arteries persists, the retina begins to suffer from subnutrition and suboxidation, and hyalin and lipids are irregularly scattered in the retina and appear in the macular area as a star figure. Arteriospastic retinopathy occurs with arterial hypertension and, with abnormal contraction and narrowing of the arteries in the brain and in the kidneys, in diffuse glomerulonephritis, in preeclampsia and eclampsia of pregnancy, in some of the less common diseases of the kidneys, and in cases of pheochromocytoma. Arteriospastic retinopathy is seen in some cases of essential hypertension after years of benign hypertension without renal insufficiency. These cases constitute an intermediate group, between the group of strictly benign cases and the group in the malignant state of hypertension. Arteriospastic retinopathy added to the arterial changes of chronic hypertension, to which papilledema is frequently added, is seen in a small group of patients with permanent renal insufficiency. These are the patients in the malignant stage of hypertension.

Some Ocular Manifestations of Prematurity. N. L. McNeil. Brit. J. Ophth. **40:**24-29 (Jan.) 1956 [London, England].

McNeil describes the functional capacities as well as the ophthalmoscopic appearances of the eyes of 16 children who had been born prematurely, most of them between 1947 and 1953. Only 2 of 32 eyes showed true retrolental fibroplasia. This indicates that the incidence of ocular defects other than presence of a retrolental membrane is more common than the presence of the membrane itself. Myopia was observed in 22 of the 32 eyes, and there seems to be no doubt that myopia is a frequent result of prematurity. Myopia occurred both with and without an associated anatomic defect and also both with and without the use of oxygen in the immediate postnatal period. None of the patients included in the series had a family history of myopia. Many of the eyes showed retinal folds (grade 3 in the American classification), the well-known end-results of the oxygenation of prematurely born children. The temporal situation of most folds and the presence on them of embryonic vessel remnants applies generally to the folds found in prematurely born, oxygenated children. Other ocular defects noted in these children were distortion of the disk and abnormal vessel patterns; gliosis of the disk; eccentric fixation associated with a functional displacement of the fixation center to the temporal side from the normal macular position; and nystagmus, which varied from a coarse searching type to a fine rapid nystagmus. Anatomic deformity of the fundus was present in all children showing nystagmus.

THERAPEUTICS

Morphine Intoxications. E. Nimb. Ugesk. læger **118:**61-70 (Jan. 19) 1956 (In Danish) [Copenhagen, Denmark].

Of 145 cases of acute intoxication with morphine or preparations with related effect, such as methadone and Pethidine, 72 were complicated with barbituric acid intoxication. Only 55% of the patients had attempted suicide. Methadone was the agent most often used, and together with morphine it caused the severest respiratory complications; Pethidine caused the fewest. Respiratory depression is the gravest symptom, but serious conditions of shock also occur. Morphine intoxication complicated with barbituric acid intoxication is on the whole more severe than pure morphine intoxication, especially because of shock. In patients with cor pulmonale, small doses of morphine can lead to grave intoxication. Children are not particularly sensitive to morphine, but codeine preparations for children must be administered with care. The combination of morphine and injectable barbituric acid preparations can cause grave intoxication even in therapeutic doses. In 48% of the cases no strict medical indication for the patient's possession of morphine was found. The mortality in morphine intoxication is higher than the mortality in all other narcotic intoxications, but in the last five years it has fallen from about 28% to about 7.5%. The prognostic significance of early hospital admission is emphasized. Therapeutically, adequate oxygen supply, maintenance of open air passages, and effective treatment of shock are stressed.

β,β-Methylethylglutarimide (Megimide) in Treatment of Barbituric Acid Intoxications. C. Holten. Ugesk. læger **118:**72-75 (Jan. 19) 1956 (In Danish) [Copenhagen, Denmark].

Of 17 cases of barbituric acid intoxication successfully treated with β,β-methylethylglutarimide (Megimide) and 2:4-diamino-5-phenylthiazole hydrochloride (Daptazole) in Aarhus Municipal Hospital since last July, 4 were grave and in 12 of the other cases the patients were comatose on admission. Two of the four cases are described in detail; the patients were brought into a safe state after treatment for 9½ and for 10 hours, with total doses of 1.35 gm. Megimide and 0.4 gm. Daptazole and 1.5 gm. Megimide and 0.45 gm. Daptazole respectively. Applied with Daptazole, Megimide has proved an active agent in barbituric poisoning and may be called a barbiturate antagonist. The possibility of convulsions during treatment with Megimide should be borne in mind, and the substance should not be given in larger doses nor more rapidly than necessary.

Respectable Hypnosis. R. Asher. Brit. M. J. **1:**308-313 (Feb. 11) 1956 [London, England].

Asher is of the opinion that the sinister notoriety with which sensational literature has endowed hypnosis has driven away many who might make good use of it. He makes a plea that it be recognized as a reasonable form of treatment in certain selected cases and that it become more respectable. He does not advocate that it be used extensively nor that physicians designate themselves as "hypnotists" or that they specialize in the subject. Hypnosis is an adjunct to treatment; it does not replace other treatments, nor does it obviate the need for examination and investigations. The powerful effect of suggestion is generally realized; a new medicine may achieve very good results by suggestion. Hypnosis means using the suggestion in pure form, without the medicine. The author has used hypnosis as an ancillary method for the last 12 years, and for the last 6 years he has devoted one outpatient session a week to it. Hypnosis is a state of exaggerated suggestibility produced by suggestion and by fixing the attention.

The author generally induces the first hypnosis in a quiet, dark room, with the patient on a comfortable couch. He asks the patient to look at a light, usually an ophthalmoscope bulb. The reason for the dark room and the light is that if there is nothing else to look at it is easier to concentrate on the one visible thing. Suggestions are made repeatedly. At the first attendance only light hypnosis may be induced, but with subsequent sessions a deeper state may be obtained each time. Certain people never go very deep, but the effect of suggestion made under light hypnosis is often nearly as good as that made under deep hypnosis. In a good subject, after the first induction it is convenient at subsequent sessions to ask him to look at some object, such as the physician's finger or a paper-knife, in broad daylight. The less ritualistic and the more straightforward the procedure the better. The patient's ideas about hypnosis seem to play little part in its production, and some patients on waking say, "Is that some sort of gas you've got in that lamp?" and have no idea that hypnosis has been used. Results are described that indicate that hypnosis may have an effect on skin diseases, including warts, excessive sweating, alopecia, and eczema. The eczema-asthma syndrome of childhood and dermatoses made worse by scratching seem specially amenable. It may be helpful, too, in psychological conditions such as hysteria, anxiety states, and obsessional neuroses.

BOOK REVIEWS

Our Blind Children: Growing and Learning with Them. By Berthold Lowenfeld, Ph.D., Superintendent, California School for Blind, Berkeley. With foreword by Herbert R. Stolz, M.D. Cloth. $5.50. Pp. 205, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, Canada, 1956.

The parents confronted with the problem of a blind child may react by exhibiting overprotection or occasionally partial rejection but in no case are they instinctively prepared for the rearing and education of an offspring so handicapped. If the blind child is to be assisted in his development toward a healthy and useful life it is necessary for the parents, after their initial psychological adjustment and acceptance of the situation, to be properly guided and informed as to their part in the adequate care of the child. This present book, written by one long familiar with the education of the blind child, describes in detail all the aspects of the training of the child afflicted with complete or partial blindness from earliest infancy through the school age. Methods of teaching necessary independence, eating, toilet training, sleeping habits, dressing, and walking and talking are all described in clear, simple language. For the school-age child there is consideration of educational placement, special classes, home-school relationships, and special methods of teaching such as the Braille writer and the talking book. Emphasis is placed on teaching self-reliance, the avoidance of undue praise but recognition of accomplishment, and the attainment of a useful place as a member of society. Since the education of the parent and his understanding of the child are essential, this book, written primarily for the lay parent, is an important contribution to the education of the blind child. It should be recommended reading not only for parents but for all social workers and teachers who have contact with these children.

Neural Control of the Pituitary Gland. By G. W. Harris, F.R.S., Sc.D., M.D., Fitzmary Professor of Physiology, Institute of Psychiatry, Maudsley Hospital, London, England. Monographs of Physiological Society, number 3. Editors: L. E. Bayliss, W. Feldberg, A. L. Hodgkin. Cloth. $6.75. Pp. 298, with 54 illustrations. Edward Arnold & Co., 41-43 Maddox St., London, W.1, England; Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

It is now evident that the pituitary gland does not enjoy the autonomous control implicit in such expressions as "the master gland" or "the leader of the endocrine symphony" by which it was formerly designated. A reciprocal relationship exists between the pituitary, as well as other endocrine glands, and the nervous system. The latter not only regulates these glands but is in turn affected by their activity. The hypothalamus in particular, through its intimate vascular connection with the pituitary, is vitally concerned in regulating hypophysial activity. Professor Harris, who has contributed much to this field, has summarized the available data in a clear and masterful manner. Presenting both sides of what in many aspects is still a controversial subject, he has objectively and critically analyzed the current experimental and theoretical aspects of the subject. He surveys the nerve and blood supply and neurovascular control of the pituitary, the transplantation of endocrine glands, the regulation of the various trophic hormones from the adenohypophysis, the anatomy and function of the hypothalamus, the nature, site of formation, and regulation of the secretion of the hormones of the posterior pituitary, and the relation of the hormones to behaviour. The book is clearly written in a simple, direct style and amply illustrated with anatomic photographs as well as helpful schematic drawings. Bibliographic references are appended to each chapter, and adequate author and subject indexes are included. This book will prove of inestimable value to physiologists generally and particularly to those engaged in research in this field. It was for these that the book was written, no attempt having been made to include the important clinical implications that are undoubtedly of great importance. The book may be recommended without reservation to those interested in this fascinating field of current physiological activity.

They Stand Apart: A Critical Survey of the Problems of Homosexuality. Edited by His Honour J. Tudor Rees, D.L., J.P., and Harley V. Usill, B.A. Contributors: The Viscount Hailsham and others. Cloth. 53.75. Pp. 220. The Macmillan Company, 60 Fifth Ave., New York 11, 1955.

The stimulus for this "critical survey of the problem of homosexuality" has come from concern over the rise in homosexuality in Britain in the past 20 to 30 years and the current interest in revising the pertinent laws. Although the increase is probably not limited to England, it is documented there by an increase of over 500% in arrests for homosexual and related offenses from 1938 to 1953. Since the phenomena of homosexuality affect society in many ways, the contributors are concerned with the legal, social, moral, and medical aspects of the problem. The book is therefore a searching survey, not a definitive evaluation, and its value lies in this. The four sections are entitled Homosexuality and the Law, Homosexuality and Society, Homosexuality and Christian Morals; Homosexuality, the Medical Aspects; Homosexuality and the Law in Other Countries; and Statistics and Abstracts from the Debate in Parliament. Each is presented in a readable and scholarly manner. Whatever the differences in opinion, the broad, reasonably objective approach is refreshing and hopeful. If the authors do no more than emphasize the confusions and injustices involved, they do a great service. It certainly becomes clear that we can no longer view the situation with fixed or limited ideas.

The section on legal history reveals that, as late as the 16th century, the offense was punishable by death. More surprising is the current existence of legislation that, although never used, makes life imprisonment possible. Everyone seems to agree, however, that prison alone is not the answer. The sections relating to society and Christian morals are of great interest and emphasize the many ramifications of the problem. For the physician concerned with diagnosis and treatment, the section on medical aspects is the least useful. The survey is on an elementary level, perhaps in keeping with the intent of the editors to reach a wide audience. It is easy to disagree with some of the reasoning and formulations, especially the author's favoring the etiological roles of organicity or constitution. (This would hardly explain the unprecedented recent increase in incidence, any more than would a theory based on early environmental influence alone.) Nevertheless, the failure of medical effort is clear; this is what makes for much of the confusion in the related fields. It is difficult for medicine to ask that legal, social, and religious pressures be removed if medicine is unable to define the causes and offer effective therapy. The final section dealing with laws in Europe (the Western Hemisphere is not included) is of special interest. The range of attitude documented is great and confused. It would be helpful if there were some way to use such a survey in tracing the effects of altered legislation on the incidence in the countries concerned. The excerpts from the debates in Parliament can be viewed only with admiration. At least there are some clear heads presenting their points of view on this explosive subject in a calm and constructive way. The problem of homosexuality is far from being solved. The position of the medical profession is excellently presented in a quotation from the *Medical Press:* "Those who lay down the law in regard to sex seem to take it for granted that we know, in fact, what is normal and healthy, whereas we only know what is customary. . . . We plead, therefore, for more research, and for the recognition of the fact that the invert is not a villain to be punished, but a patient to be studied—to our own ultimate advantage."

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

QUERIES AND MINOR NOTES

ACCIDENTS WITH ROTARY-TYPE LAWN MOWERS

To the Editor:—*Are there any data on the incidence of injury caused by rotary lawn mowers? I refer to the possibility of the blade breaking and fragments being thrown at high speeds.*

V.M.D., New York.

Answer.—In May, 1954, the Association of Casualty and Surety Companies issued a bulletin on rotary-type lawn mowers in which it was stated: "The Rotary type lawn mower has gained increasing popularity in recent years. Unfortunately, along with this increase in usage there has been an alarming number of serious accidents involving both operators and persons in the vicinity. This type of mower usually operates at speeds in excess of 2,400 revolutions per minute. Power to rotate the cutting blade is supplied either by a gasoline or electric motor. While the cutting blade rotates under a shield or cover, openings in the front and rear are necessary to permit efficient cutting and discharge of the cut grass. Generally no mechanical means are provided for moving the mower about the lawn. According to data accumulated, accidents have been caused by sections of cutting blades being thrown from blade arms, pieces of cutting blades breaking off, blades picking up and throwing pieces of stone, wire, etc., and operators' feet and hands coming in contact with revolving blades. In the case of electrically operated mowers, defects in the switch, cord or motor may expose a person on wet ground to electric shock." Another portion of this bulletin is devoted to comment on the safe operation of rotary lawn mowers. *Consumers' Research Bulletin* for July, 1955, page 26, comments on rotary lawn mower accidents and cites one instance wherein a broken blade was propelled across a street and killed a woman.

SEVERE REACTION TO PENICILLIN

To the Editor:—*In a person who has recovered from a severe allergic shock occurring immediately after an injection of penicillin S-R, would a future injection of the same drug cause immediate death? What are the dangers of working around penicillin? In the case of an accidental contact through the broken skin, what amount of penicillin will precipitate another reaction, and of what nature? Is there danger of sensitization to procaine anesthetics, even though the procaine in the penicillin is of a different chemical status?*

M.D., Illinois.

Answer.—It is assumed that the reaction of the patient described was an anaphylactic one in which respiratory difficulty and shock became evident within a few minutes after injection of fortified penicillin (aqueous mixture of soluble penicillin and suspension of procaine penicillin). There would be real danger of death from a future injection. Fatalities after penicillin injections have been reported in individuals with previous nonfatal reactions. There would be danger from local contact with penicillin; the chance of anaphylactic reaction and death, particularly with a small amount, would be less than with parenteral injection (apt to be a considerably larger amount) but would be present along with the danger of local reactions. Procaine has not been shown to be a significant factor in anaphylactic reactions to procaine penicillin, and the individual is probably sensitive to penicillin; however, contact with procaine should be avoided, if possible, and sensitivity tests performed if the individual's occupation (medicine, dentistry) might require some contact.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

BLEEDING AFTER URINATION

To the Editor:—*A 61-year-old man has had bleeding for one month whenever he finishes urinating and pain in the left ischial region for several months. There are no nodules in the prostate and a 22 sound was passed without difficulty. A series of prostatic massages, done twice weekly for three weeks, has not relieved the condition, and bloody secretion is consistently expressed by massage. Papanicolaou stain shows no cancer cells. The patient has received Furadantin and Gantrisin. Is any other therapy indicated? Should the massages be continued?*

M.D., Arizona.

Answer.—No mention is made in regard to this patient of any bacteriological studies of either the urine or the expressed prostatic contents. Terminal hematuria is common in chronic prostatitis, but the patient, according to what is gathered from the question, has not been completely studied. A cystoscopic and urethroscopic examination is certainly indicated to rule out any possibility of neoplasm, either in the urethra or bladder, and any possible mechanical condition that might be contributing to a disturbance of the neck of the bladder. Massages should not be continued unless they are based on realistic findings. This patient should have a urine culture, both before and after prostatic stripping. He should then have urethroscopic and cystoscopic examinations, and, possibly, a cystogram and urethrogram should be taken before continuing a prolonged series of treatments that are not necessarily aimed at a definite condition.

ALOPECIA AREATA

To the Editor:—*A 29-year-old white woman was operated on for ruptured extrauterine pregnancy in 1954. This was followed by depression and loss of scalp hair in spots. She was treated by a specialist with some improvement but has gotten worse recently, with hair coming out in spots and recurrence of depression. What treatment would be advisable?*

M.D., South Carolina.

Answer.—The description of the hair loss suggests the diagnosis of alopecia areata. Emotions in some indirect manner are thought to play a causative role, but the connection has not been proved. The treatment is one of stimulation to the scalp, either by hand massage, electric apparatus, or ultraviolet rays, or by the application of a stimulating ointment. The condition sometimes corrects itself without treatment. It would seem that psychiatric opinion should be had for this patient.

FUMIGATION OF GRAIN AND FLOUR

To the Editor:—*Is there knowledge of any cerebral thrombosis that has occurred in people who have worked with the gas methyl bromide, or EB 15, for fumigation of mill grain and flour? A patient developed a peculiar peripheral neuritis that cleared up, but he later developed a disability in the use of the right hand and a speech aphasia. This patient insists that he has heard of cases such as this occurring in grain mills, but I have been unable to find anything in the literature.*

M.D., Nebraska.

Answer.—Methyl bromide is a profoundly toxic industrial agent attacking many organs and systems but with predilection for pulmonary and nervous system tissues, with emphasis on the former. Hemorrhage within the central nervous system and thrombosis become a possibility. Next to visual disturbances, speech dysfunction dominates the clinical picture in those cases with central nervous system involvement. While thrombi and emboli are a prospect, it is possible that the inquirer overstressed their significance. Severe damage may arise in their absence. Methyl bromide victims are prone to psychological reactions, with neuroses becoming in the long, drawn-out cases more difficult to eradicate than organic damage. The rule is in

nonfatal cases that reversible processes eventuate in full recovery. An essential part of therapy is to guide the patient away from long, persistent functional residuals. Johnstone (*Indust. Med.* **14**:495, 1945) describes 34 cases arising from a fumigating process.

TREATMENT OF CYSTOCELE

To the Editor:—*Please give the accepted surgical treatment for a marked cystocele in a 70-year-old woman who is a "good surgical risk" except for a blood pressure of 180/100 mm. Hg. The rest of the cardiovascular and kidney status is normal. The cervix can be seen just within the ventral orifice. Should a vaginal hysterectomy or a simple vaginoplasty be performed?*

M.D., New York.

Answer.—There is no need to perform a hysterectomy in order to cure a cystocele or even a prolapse. An extensive plastic operation should suffice in this patient. However, a curettage should be done before the plastic operation, to rule out malignancy. The repair can easily be done under direct infiltration anesthesia, but epinephrine should be omitted from the local anesthetic solution because of the hypertension.

DILATED VEINS OVER THORAX

To the Editor:—*Of what significance, if any, are dilated veins, without edema, in front of the chest in case of intrathoracic pathology?* *Alfred R. Ross, M.D., Fort Bliss, Texas.*

Answer.—Many people have slightly dilated veins over the anterior thorax all of their lives. These are of no clinical significance. If the veins have appeared recently in association with mediastinal pathology, they are usually evidence of vena caval obstruction caused by a malignancy. Benign tumors rarely cause obstruction of the vena cava.

WHITFIELD'S OINTMENT

To the Editor:—*Please furnish the original reference to Whitfield's ointment, as there are many preparations of varied composition that pass for it.* *M.D., Maryland.*

Answer.—The original reference to Whitfield's ointment appeared in the *British Journal of Dermatology* (**23**:35-39, 1911). The ointment consists of 5% benzoic acid and 3% salicylic acid contained in one part soft paraffin and three parts coconut oil.

ATYPICAL FACIAL NEURALGIA

To the Editor:—*Please discuss the treatment and prognosis in primary atypical facial neuralgia (Sluder's neuralgia) in a 30-year-old woman. Pain was temporarily relieved by cocainization of the nose and procaine infiltration of the sphenopalatine ganglion, but no relief was obtained from infraorbital nerve block.* *M.D., North Dakota.*

Answer.—There is no evidence that either atypical facial neuralgia or Sluder's neuralgia constitutes a medical entity. There are various forms of atypical facial neuralgia. Some of these are on a vasomotor basis, and in other instances the physical basis for the pain is unknown. In view of this ignorance regarding the etiology of these distressful conditions, it is not surprising that there is no single satisfactory form of treatment. Many different treatments have been tried, with varying degrees of success.

AFRICAN TRYPANOSOMIASIS

To the Editor:—*Does African trypanosomiasis occur in South Africa?* *M.D., California.*

Answer.—Human trypanosomiasis does not occur in the Union of South Africa. The distribution of Glossina indicates only the presence of G. pallidipes or G. brevipalpis in the northeast on the coast line. Human trypanosomiasis has been reported in the territories of Mozambique, Bechuanaland, Northern Rhodesia, Southern Rhodesia, and Angola. Prior to 1896 G. morsitans did occur in the northern Transvaal but disappeared at the time of a disastrous outbreak of cattle plague (rinderpest), which swept through the country in that year. However, no record of human trypanosomiasis having been associated with the occurrence of this species exists, although nagana in domestic stock was rife in some areas. In Zululand there is no evidence to suggest that G. morsitans ever occurred there, the species associated with nagana in stock comprising G. pallidipes, G. brevipalpis, and G. austeni. No evidence of human infection has ever been found.

BILATERAL URETERAL CATHETERIZATION

To the Editor:—*In* The Journal, *May 5, 1956, page 118, two consultants replied to a query on the advisability of bilateral catheterization of the ureters to minimize the danger of ureteral damage when moderately difficult total hysterectomies are to be performed. I agree with the first consultant as far as he goes, but I go much further. I believe that to avert ureter damage ureteral catheterization should be carried out in all cases where hysterectomy is to be performed. I have seen cases where ureters were injured, kidneys lost, and fatalities occurred in the course of total, subtotal, and vaginal hysterectomies; and these complications happened not only to tyros but to chiefs of staff in teaching institutions. I am in total disagreement with the other consultant, who states that he does not catheterize the ureters at all in pelvic surgery because, as he says, whenever doubt exists in difficult cases the ureters should be identified abdominally. I have witnessed operations by world-renowned surgeons where search for the pelvic portion of the ureters consumed considerable time and in at least one instance was entirely unsuccessful. As to his statement that catheters, being stiff, tend to push the ureters one way or another and may enhance the danger of trauma, my experience is entirely contrary to his. No. 6 ureteral catheters can be readily palpated throughout the course of the operation, and injury to the ureters in these circumstances should be rare. I have records of 126 cases in which bilateral ureteral catheterization was performed. I operated on the majority of these patients; the remaining operations were performed by residents or members of my staff. The results have been most gratifying. Ureteral catheterization adds only an average of six minutes to the operating time, but it adds greatly to the surgeon's peace of mind, for he can feel pretty sure that his patient will leave the hospital with an intact urinary tract.*

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To the Editor:—*On the subject of preoperative bilateral ureteral catheterization* (The Journal, *May 5, 1956, page 118), I have just reported, at a urologic section meeting, a series of patients who had sustained urinary tract injury during gynecologic surgery performed by experienced and competent surgeons. In the course of preparation of this report, study of the literature revealed an astonishingly high incidence of reported ureteral and bladder injury, considering that most cases do not find their way into print. Certainly, catheter insertion is not a substitute for meticulous surgery, which includes adequate incision and exposure, no blind clamping or cutting, visual observation of the vessels and ureters, and no "pawing in a bloody well." However, catheters do not create morbidity, they are a legal protection, and presence of a catheter will facilitate ureteral repair if required. It will also represent an inlying splint as well as a drain in cases where trauma, distortion, or partial suture obstruction to the ureter occurs. The inlying ureteral catheter is not always easy to palpate, especially if the adjacent tissues are indurated, but the routine use of ureteral catheters has practically stopped accidental injury. Surely, when a relatively simple and innocuous procedure, such as elective hysterectomy, can be complicated by preventable mutilating and dangerous sequelae, every measure that can prevent these complications should be utilized, even by "one qualified to do pelvic surgery."*

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